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Edited by ROBERT A. STRONG, M. D.
with the collaboration of
FREDERICK TICE, M. D.
IRVINE McQUARRIE, M. D.
MAXWELL M. WINTROBE, M. D.

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International Medical Digest

Volume 57 AUGUST, 1950 Number 2

General Medicine

Deoxycortone and Ascorbic Acid in the Treatment of Rheumatoid Arthritis — BYWATERS, E. G. L., DIXON, A. ST. J. AND WILD, J. B. — *Lancet*, 1: 951 (May 20) 1950.

In view of their failure to observe any obvious bedside improvement in patients with rheumatoid arthritis after the injection of ascorbic acid and deoxycortone acetate, following the technique recommended by Lewin and Wassén, and in view of the numerous claims that such improvement does result, the writers have followed 10 patients more closely, with statistical analysis of some of the responses.

"Criteria for selection of patients included an erythrocyte sedimentation rate above 25 mm. in 1 hour (Westergren), and radiological signs of bone and cartilage destruction. The disease had been present for 1 to 10 years.

"Assessment included, besides an inquiry into symptoms, and a daily diary kept by 4 of the patients: (*a*) measurement of strength of grip in mm. Hg (in patients with wrist involvement); (*b*) measurement of the angles of flexion and extension of the knees or other involved joints; (*c*) assessment of pain on pressure over a joint (graded 0-3); and (*d*) functional tests, such as the measurement of time to put on or take off a certain garment, walk a certain distance, or write a test sentence, or of the number of stitches knitted in two minutes. The angles of the knee movement were measured in duplicate. Two strips of wood, hinged together at one end, were aligned with bony points (marked in indelible ink) on the outer malleolus, outer condyle of tibia, and greater trochanter. The angle was then drawn on paper and was measured later. This ensured a 'blind' measurement. Direct eosinophil counts were done 3 hours after the injection."

"The plan of the first experiment was as follows:

"After preliminary familiarisation of the 3 patients with the methods of measurement, and a week or so under hospital conditions, an injection (of a substance unknown to the patient) was made at 10:55-11 A.M. each day, preceded by a battery of measurements at 10:15 A.M. and 10:45 A.M. and followed by the same measurements at 11:15 A.M. and again at 11:45 A.M. The substances used were saline intravenously (2 ml.); procaine intravenously (4 mg. per Kg. body weight in 200 ml. of saline in 20 minutes); and deoxycortone acetate 5 mg. intramuscularly (or 5 mg. of the glucoside intravenously) and ascorbic acid 1 Gm. intravenously.

"The results showed no significant change after either saline, procaine, or deoxycortone acetate and ascorbic acid." Representative readings, given in table 1 show three replications of each type of treatment in 1 of the 3 patients. "Evaluation was by the ratio of the difference between the means of each measurement before and after each type of drug to the standard error of that difference. Values of t were obtained for saline, deoxycortone, acetate and ascorbic acid, and procaine well below the minimum required for $p=0.05$. No significant change in eosinophils was seen.

"Because there was some day to day variation in base line readings, which might have masked small but significant differences, a second experiment was made, of a Latin square design, where 3 patients with hand and wrist involvement had three different treatments (saline, deoxycortone acetate and ascorbic acid, and procaine) on each of three different days. Readings of hand grip were made in duplicate before and one hour after each injection. Changes in left and right grips after injection showed no significant difference and hence were treated as two further replications. An

Table 1.—Immediate Effects of Deoxycortone Acetate and Ascorbic Acid Injection, Compared with Procaine and Saline

Injection	Walking time (sec.)		t*
	Before	After	
Saline	50.0±6.3	48.5±7.6	0.3
Deoxycortone acetate and ascorbic acid	57.0±4.3	52.0±4.8	1.9
Procaine	47.3±5.5	44.5±4.6	1.3

*2.45 for p=0.05.

Similar findings with left-handed and right-handed strength, knitting time, and eosinophil count.

analysis of variance (with 35 degrees of freedom) showed that neither the variance between persons, days, or treatments reached significance. This whole trial has been repeated once again with the same patients, the same treatments (except that the dose of procaine was doubled), and the same results.

"Independent analyses by two observers of the diary kept by the most reliable of the patients treated and the most 'objective' self observer, showed remarkable agreement. There was little difference between the effects of procaine, saline, and deoxycortone acetate and ascorbic acid. Thus of the 18 days of the trial, moderate improvement was noted on 3 days (2 of which followed procaine and 1 deoxycortone acetate plus ascorbic acid); on 6 days slight improvement was noted (4 following deoxycortone acetate and ascorbic acid and 2 following saline). No change occurred on 8 days (following procaine on 3 days, saline on 4 days, and deoxycortone acetate and ascorbic acid on 1 day). She became worse on 1 day only (following procaine). Although there was some relationship between objective and subjective improvement, this was not constant. The highest grade of subjective improvement coincided on only 1 day with the highest grade of objective improvement, and that followed a procaine injection. The patient left hospital after 7 weeks greatly improved—as she had done also after her previous admission in 1948.

"Three cases of established rheumatoid arthritis in children were studied in respect of numerous functions before and after injections of saline, and of deoxycortone acetate and ascorbic acid. No significant objective change occurred i either the clinical observations or the meas ured functions. One of these patients ha previously shown a good response t adrenocorticotropic hormone (ACTH (which had also, of course, been substi tuted after an 8 day control period o saline injections)."

A longer trial of deoxycortone acetat and ascorbic acid in 3 patients with rheu matoid arthritis was made. Observation were made on a patient who had had rheu matoid arthritis for 4 years. All criteri improved on the first few days of salin injection, and no further improvement oc curred when deoxycortone acetate an ascorbic acid was substituted (given thre times daily for 3 days). "Two other pa tients, studied in the same way, showe exactly the same results."

Finally, the writers have administere deoxycortone acetate and ascorbic acid o 3 days, and saline on 3 days, to a patien with severe rheumatoid arthritis who ha previously undergone an immediate an dramatic remission with ACTH and wh had relapsed after cessation. "The patien had a very good idea what subjective im provement he might expect, but neithe subjective nor objective improvement wa noted in either degree or rapidity of join movement."

Conclusion.—The writers are well awar that statistically negative results like th do not prove that the treatment is witho effect; the wrong criteria may have bee selected. In their trials of ACTH, a numbe of criteria have shown no significan change; other criteria have shown signifi cant improvement. The writers think tha in the present cases, however, any re

improvement, even if unnoticed by the patient or by the observer, would have been revealed by the several tests that they chose.

They conclude, therefore, from this limited but intensive experience that deoxycortone and ascorbic acid has no immediate measurable or appreciable effect on rheumatoid arthritis beyond that which follows any nonspecific injection or treatment, and that it is not in any way comparable to ACTH.

The Clinical and Metabolic Effects of Progesterone and Anhydrohydroxyprogesterone in Rheumatoid Arthritis — KYLE, LAURENCE H. AND CRAIN, DARRELL C. — *Annals of Internal Medicine*, 32: 878 (May) 1950.

"Fourteen patients with active rheumatoid arthritis have been treated with progesterone or anhydrohydroxyprogesterone for periods of 12 to 40 days. . . . This study was predicated on the basis that increased blood levels of progesterone might be the factor responsible for the remission of symptoms in patients with rheumatoid arthritis, not only in pregnancy but also in hepatitis and jaundice." The results are essentially negative.

Cases were selected to allow adequate distribution with respect to age, sex, severity of joint involvement and chronicity of the disease. "All the patients had typical features of rheumatoid arthritis and were studied during an active phase of the disease. The greater number were hospitalized on the metabolic ward; a few were followed in the outpatient clinic. Progesterone (Lutocylin) was given by intramuscular injection to the majority of the patients, while those treated as outpatients were given anhydrohydroxyprogesterone (Lutocylol) by mouth. Both drugs were used in 4 of the patients. The dose was calculated on the basis of the amount of pregnandiol excreted in the urine at the time of pregnancy when remission of arthritic symptoms is most prone to occur; i.e., after the third month, at which time 15 to 20 mg. of pregnandiol is excreted daily. Although this substance is equivalent to progesterone, molecule for molecule, at least 50 per cent is believed to be lost in the extraction process. Consequently, 40 mg. of progesterone were deemed necessary and a dose of 50 mg. was chosen as that which would give a margin of safety in equalling normal physiologic levels of circulating hormone during pregnancy." Inasmuch as it was found that less than 50 per cent of administered progesterone is recovered as pregnandiol, a number of patients were given 100 mg. of progesterone daily. "Because of the knowledge that the effect of injected progesterone is short in duration, therapy was administered at least daily and usually in two daily doses. On the assumption that anhydrohydroxyprogesterone is at best one fifth as potent as the intramuscular preparation, 200 mg. was chosen as the minimal daily dose necessary to achieve any therapeutic effect." Following the report of the successful use of cortisone in the treatment of arthritis, 2 patients were treated with larger doses of progesterone by injection; i.e., 150 and 200 mg. a day, respectively.

"All of the patients were followed for a control period prior to the institution of treatment. The clinical severity of their disease was measured in respect to pain, stiffness, swelling and limitation of motion, quantitation of these symptoms being recorded by two observers as well as the patient. Similar clinical evaluation was conducted throughout the period of therapy and for varying lengths of time thereafter. Several patients were followed carefully by the physical therapy department with measurement of active and passive movement of the affected joints before, during and after therapy. Administration of an inert placebo was conducted in those patients who showed definite clinical improvement while on progesterone with relapse after the withdrawal of medication."

"Numerous laboratory studies were conducted, but there was no relationship between clinical improvement and change in the laboratory findings."

"Case Reports.—Case 1: A 44 year old white male with peripheral rheumatoid arthritis of six years' duration had experienced numerous acute episodes with redness, swelling and progressive deformity, and his disease had been increasing in severity for the year prior to hospitalization. Previous therapy had included intra-

venous typhoid vaccine, intravenous novocain, numerous transfusions and gold. He was hospitalized on the metabolic ward and after a control period of eight days was given 50 mg. of intramuscular progesterone daily. During and following this treatment he showed no improvement and the sedimentation rate, which was moderately elevated, showed some increase during therapy.

"Case 2: A 39 year old white male had rheumatoid arthritis and rheumatoid spondylitis of two and one-half years' duration. Initially, the peripheral joints were actively inflamed and reddened, but at the time of study there was chronic deformity with only moderate acute inflammatory reaction. He had previously received the usual types of therapy including x-ray to the spine and chrysotherapy for the peripheral joints. For six months prior to hospitalization, his condition had been steadily deteriorating. After a control period of eight days he was given 50 mg. of progesterone intramuscularly daily for 20 days. There was no appreciable clinical improvement. His sedimentation rate was moderately elevated, and although there was a drop to within normal limits in the early phase of treatment, the rate had returned to the control level before therapy was concluded.

"Case 3: A 41 year old white female with peripheral rheumatoid arthritis of approximately 10 years' duration had been going steadily downward for several months prior to treatment and showed both acute inflammatory reaction and chronic deformities of various joints. She had received routine therapy including gold without effect. Fifty milligrams of progesterone were given daily for 22 days, followed by the oral preparation of anhydrohydroxyprogesterone, 150 mg. daily, for one week. Although there was some increase in motion of the arms, the symptoms of acute inflammation became more severe. The sedimentation rate was very high and remained elevated throughout her course. She was again seen one month after the completion of therapy at which time there was no change, and for the past year her condition has steadily progressed in severity.

"Case 4: A 37 year old colored female with progressive rheumatoid arthritis of two years' duration had manifested continuous rheumatic activity with limitation of motion, pain and moderate swelling involving particularly the elbows and fingers, throughout this two year period. The administration of progesterone, 50 mg. daily for 25 days, resulted in marked clinical improvement but there was no appreciable change in the definitely elevated sedimentation rate and no more than slight measurable increase in motion of the affected joints. Within one week after discontinuation of treatment, mild symptoms recurred and within one month these had increased to the degree of original severity. Three months after the termination of the first course of therapy, at which time the symptoms had become markedly increased in severity, she was treated in the outpatient department with 200 mg. of anhydrohydroxyprogesterone daily for 25 days. A marked clinical response ensued which has been maintained for the past nine months, preventing the administration of placebo medication. The sedimentation rate has remained markedly elevated throughout this period of time.

"Case 5: A 73 year old white male, with rheumatoid arthritis of approximately 11 months' duration, showed, early in the course of his illness, recurring attacks of pain and swelling which suggested the diagnosis of palindromic rheumatism. Five months prior to admission the acute attacks failed to subside and he showed increasingly severe pain, swelling and limitation of motion in the hands and wrists. After a 12 day period of study on the ward, he was given 100 mg. of progesterone by injection for 18 days. After 10 days of therapy there was some subjective improvement and at the time of completion of treatment, although there was only slight increase in motion, the pain and swelling were less prominent. Two weeks later the symptoms recurred with the original degree of severity. His sedimentation rate was markedly elevated and showed no significant change during or after therapy. The patient did not believe that a second course of treatment would be worth while and consequently no placebo could be administered.

"Case 6: A 19 year old white male with very severe rheumatoid arthritis and rheumatoid spondylitis of six years' duration

had had steady progression of the disease from the time of onset. Previous therapy had included x-ray, intravenous typhoid vaccine, Ertron, gold and synovectomy of one knee. At the time of admission to the hospital there was rigidity of the entire spine and deformity of most of the peripheral joints. An acute reaction was present in one wrist and knee. He was given 300 mg. of anhydrohydroxyprogesterone for 25 days and then 50 mg. of intramuscular progesterone for 14 days. No clinical change could be demonstrated. The blood sedimentation rate varied between moderate and mild elevation during treatment, but was elevated to a considerable degree at the time therapy was discontinued.

"Case 7: A 39 year old white woman had been suffering from rheumatoid arthritis for 20 years. Originally the involvement had been intermittent, but for three years she had shown persistent activity with gradually increasing deformity of the hands and feet. At the time of study, the patient had moderate activity of the disease with pain on motion and tenderness of hands and feet. She was given 300 mg. of anhydrohydroxyprogesterone daily for 10 days and 100 mg. of progesterone intramuscularly for 15 days. There was some slight degree of improvement in pain and stiffness which continued for three weeks after completion of treatment. The sedimentation rate was elevated and showed little change until near the completion of therapy at which time it showed some decrease. Two weeks after discharge, at which time the clinical improvement was even more manifest, the sedimentation rate was found to be markedly increased.

"Case 8: A 50 year old white female had had rheumatoid arthritis for four years. The original episode was characterized by an intense inflammatory reaction in the joints which subsided after gold therapy, leaving some residual deformities in the hands and fingers. About seven months before admission, there was a severe recurrence of symptoms continuing up to the time of study. She was admitted on the metabolic ward and given 300 mg. of anhydrohydroxyprogesterone daily for 28 days. Some improvement in stiffness and swelling occurred, but pain and limitation of motion remained essentially unchanged. This was maintained for several weeks, but two months after discharge the disease had resumed its progressively downward course. The markedly elevated sedimentation rate showed no decrease during or following therapy.

"Case 9: A 16 year old white girl had rheumatoid arthritis of five years' duration. There had been temporary improvement following a course of typhoid vaccine therapy, but no effect was evident after a second course or after treatment with gold, massive doses of vitamin D, physical therapy or repeated transfusions. Her course had been steadily progressive for one and one-half years prior to admission, and at the time of study there was marked involvement of the knees, fingers and elbows with pain, tenderness, and limitation of motion. She was treated with 150 mg. of intramuscular progesterone daily for 10 days. At the time of completion of therapy there was slight relief of pain, some increase in joint movement and minimal decrease in swelling, but two weeks following treatment the acute symptoms recurred. The sedimentation rate was markedly elevated and remained so throughout the course of treatment.

"Case 10: A 25 year old white female first developed symptoms of rheumatoid spondylitis approximately 10 years ago. Involvement of the peripheral joints had been present for three years. At the time of this study there was complete ankylosis of the spine and signs of activity in the form of redness, swelling and pain in several of the peripheral joints. The patient was given progesterone intramuscularly, 150 mg. daily for 3 days and 200 mg. daily for 12 days. During the last 7 days of therapy 800 to 1,000 mg. of ascorbic acid were given daily both by vein and by mouth. There was only minimal clinical improvement and the markedly elevated sedimentation rate remained unchanged.

"Case 11: A 52 year old colored female had rheumatoid arthritis of 12 years' duration. At the time of this study, she had residual thickening of both wrists with almost complete immobility. There was fusiform swelling and tenderness of the left middle finger and painful limitation of motion of the left shoulder. She was given 150 mg. a day of anhydrohydroxyprogesterone for 14 days. There was marked clinical improvement including freer move-

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"Case 2: A 39 year old white male had rheumatoid arthritis and rheumatoid spondylitis of two and one-half years' duration. Initially, the peripheral joints were actively inflamed and reddened, but at the time of study there was chronic deformity with only moderate acute inflammatory reaction. He had previously received the usual types of therapy including x-ray to the spine and chrysotherapy for the peripheral joints. For six months prior to hospitalization, his condition had been steadily deteriorating. After a control period of eight days he was given 50 mg. of progesterone intramuscularly daily for 20 days. There was no appreciable clinical improvement. His sedimentation rate was moderately elevated, and although there was a drop to within normal limits in the early phase of treatment, the rate had returned to the control level before therapy was concluded.

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ment of both wrists which at the beginning of therapy were believed to be permanently ankylosed, but no change occurred in the elevated sedimentation rate. Improvement remained manifest for the next several months despite laboratory evidence of continued activity. About one year after this treatment was given she had an acute exacerbation of symptoms, and an inert placebo was administered. A prompt clinical remission occurred which was manifest for the next three weeks. Treatment was discontinued with prompt return of symptoms and again there was relief after the institution of placebo treatment. At no time during this patient's course was there any depression of sedimentation rate which would suggest a true remission of her disease.

"Case 12: A 60 year old white female had arthritis of 30 years' duration. Over this period of time she had experienced numerous acute attacks of arthritis involving the joints of all extremities, each one leaving her with a greater amount of residual deformity. At the time of study, in addition to the chronic deformities the patient had an acute involvement of both hands, the left wrist and both knees. She was treated for 21 days with 200 mg. of anhydrohydroxyprogesterone. There was no clinical improvement and the markedly elevated sedimentation rate remained essentially unchanged.

"Case 13: A 60 year old white male had had rheumatoid arthritis for approximately 15 months. Prior to progesterone therapy he had received intravenous typhoid vaccine and gold without appreciable benefit despite the fact that the gold had produced a severe dermatitis. At the time of progesterone therapy there was acute involvement with redness, swelling and tenderness of practically all peripheral joints. He was given 200 mg. a day of anhydrohydroxyprogesterone and after a few days of therapy there was quite marked clinical improvement. This improvement continued for the next two and one-half weeks although the sedimentation rate remained markedly elevated. After 18 days an inert placebo was substituted. Improvement continued on this regimen, but when the placebo was discontinued for a few days a prompt and moderately severe exacerbation of symptoms occurred. Again there was improvement when placebo therapy was resumed which continued for the next three weeks. At no time was there any material change in the markedly elevated sedimentation rate.

"Case 14: A 37 year old white woman's disease had commenced four years before with involvement of the hands. The condition progressed to involve the knees, toes, ankles and shoulders and for the six months prior to this study there had been steady progression with little effect from a short course of gold therapy. At the time of study, there was acute involvement of the left ankle and knee which were swollen, red, hot and tender. The patient was given anhydrohydroxyprogesterone 200 mg. daily for a total of 25 days. No clinical improvement resulted and there was some increase of the markedly elevated sedimentation rate. She has gone steadily downward since that time and her active disease has persisted. A course of gold, given several months after the progesterone therapy, proved to be equally ineffective in controlling her symptoms.

"None of the patients showed any toxic symptoms except for case 10 who received the largest dose of progesterone. This patient noted that there was some loss of head hair after the completion of treatment. There was no clinical evidence of fluid retention, and little gain of weight in any case. No unusual or unexpected menstrual changes occurred except in 2 patients. Case 4 had a normal expected period while receiving a daily dose of 50 mg. of progesterone. This patient was the only one to show any marked clinical improvement. One other patient, case 10, had been amenorrheic for several months following a course of x-ray therapy for her spondylitis, and the vaginal smear showed lack of any estrogenic effect. A few days after the completion of progesterone therapy, she had vaginal bleeding which simulated a normal menstrual period. Two of the patients believed that their appetites were markedly stimulated by the medication, but as both these patients were on controlled food intake for balance study this symptom could not be objectively evaluated. No patient showed any statistically significant change in blood pressure."

Suggested Mode of Action of Corticotrophin in Rheumatoid Arthritis and the Allergic State—GREEN, H. N. —*British Medical Journal*, 1: 1165 (May 20) 1950.

"One of the many side issues early brought to mind by the study of shock as the general reaction to tissue injury was the relationship of the shock reaction to all the various types of tissue insult which had been reported to ameliorate the symptoms of rheumatoid arthritis."

"A rather unexpected link-up has now appeared following apparently unrelated studies on the shock reaction." In view of the hyperglycaemic state in the early stages of shock and the observation that the injection of starch or glucose strongly accelerates the rate of skin mitosis, the effect of shock on skin mitosis was studied. "At the very beginning of the general bodily reaction, induced by the release of limb tourniquets or the injection of ATP. into the mouse, mitosis in the skin ceases entirely, or is much depressed, for at least seven hours. The injection of glucose, which strongly reinforces the existing hyperglycaemia, does not influence this inhibition in the slightest. Some facts were given in support of the hypothesis that a metabolite or metabolites from the post-ischaemic limb, and also injected ATP., interfere with carbohydrate utilization, possibly indirectly through a hormonal mechanism, and thus prevent mitosis. The anticipated hormonal mechanism was via the pituitary-adrenocortical route.

"Effect of ACTH on Skin Mitosis.—This has now been put to the test indirectly by observing the effect of ACTH on skin mitosis in the mouse under precisely similar conditions to those used in the shock experiments. Following the subcutaneous injection of 1 mg. of ACTH, skin mitosis was depressed for several hours in a similar way to that observed in postischaemic shock."

"The rate of skin mitosis is probably only a reflection of mitotic activity in many other tissues, though not necessarily in all, and the well known effect of ACTH and the 11-oxysteroids in producing lymphopenia and involution of lymphoid tissue may therefore be due to direct suppression of lymphocyte production rather than to accelerated destruction. The same considerations apply to the general inhibition of body growth, the eosinopenia, the failure of granulation tissue formation, the inhibition of chondro-osteogenesis, etc. —all well known features of ACTH activity.

"The immediate depression, or suppression, of mitosis in the formative cells from which the lymphocytes and other antibody-producing reticuloendothelial cells are derived may in itself depress or abolish the tissue antigen-antibody reaction and the resulting allergic inflammatory reaction. This would account for (1) the suppression not only of the local but also of the general effects of this reaction because of the failure of histamine and most probably other by-products of the reaction to appear, and (2) the nonspecific nature of the ACTH-adenal-glucocorticoid mechanism, for on this basis temporary depression of all allergic tissue reactions, however produced, should result. It would also account for the rise in uric acid and nitrogen excretion, for on this hypothesis the temporary halt in nucleoprotein synthesis should lead to the accumulating purines and amino acids being excreted in excess by the normal paths. On this basis also the accelerated glucogenesis following ACTH treatment might in part be explained. The hypothesis would also explain the more rapid spread of an infected focus in the tissues under the influence of ACTH or cortisone.

"The Role of Allergy.—The suggested mode of action of ACTH in rheumatoid arthritis and the other clinical states in which it is active does not necessarily imply that any or all of these are in fact manifestations of excessive tissue allergy." Since the writer first studied shock experimentally, evidence for the role of allergy in rheumatoid arthritis has to him always seemed strong, because extensive tissue damage of any kind depresses metabolism generally, and one might therefore expect a depression of antibody formation. "The explanation of the therapeutic action of heavy metals as a blocking of the reticuloendothelial system, and the occasional favourable results of splenectomy, fit in well with this conception. However, even if the allergic hypothesis is not correct, the tissue lesions still remain, from

the pathologist's standpoint, inflammatory in nature, and without cellular proliferation they could not appear. Even the proliferation of malignant cells is in some instances depressed by ACTH, for there are now reports that this treatment induces temporary remissions in acute leukaemia." However, several writers have recently given convincing evidence that ACTH and cortisone decrease tuberculin hypersensitivity in the guinea pig. "It would therefore not be surprising if a striking general as well as local improvement following this treatment proves to be an indication that a hypersensitive state exists.

"While temporary failure of local lesions to appear could be accounted for, purely on the antimitotic hypothesis, in those diseases where a striking general clinical improvement also occurs it would be difficult to explain without supposing that the general manifestations, including the raised blood sedimentation rate, are not induced by by-products (including gamma globulins) of the hypersensitive reaction in strongly predisposed tissues. In nonallergic bacterial inflammation, in spite of suppression of the local tissue reaction, general improvement should not occur, except perhaps very fleetingly, but rather the reverse, since spread of the local infection would be facilitated."

Veratrum Viride and Essential Hypertension — WILKINS, ROBERT W. — *New England Journal of Medicine,* 242: 535 (April 6) 1950.

"*Veratrum viride* is effective in moderating the arterial pressure in essential hypertension."

"The hypotensive effects of *V. viride,* whether crude root, purified extract or pure alkaloid, are apparently similar in normal animals, normal human beings and hypertensive patients. Generally vasodilator, these effects may be mediated through the central nervous system. . . . Salivation, nausea and vomiting are the most frequent of the unpleasant side effects, and circulatory collapse the most alarming—though usually an innocuous—evidence of overdosage of the drug. As antidotes for these reactions, atropine (0.5 to 1.0 mg.) or ephedrine (30 to 45 mg.) or both have been given intramuscularly."

As for its specific hemodynamic effects in man, studies in the writer's laboratory have shown that during the hypotensive response to *V. viride* cardiac output does not decrease but, on the contrary, may increase, particularly in patients with reduced cardiac outputs due to hypertensive cardiac failure. "In no sense sympatholytic, the drug leaves the vasomotor reflexes and postural adaptations intact. Although renal blood flow initially may decrease with the first sizable fall in arterial pressure after administration of the drug, it returns to control values when the pressure becomes stabilized at the lower levels. Blood flow through the portal circuit of the liver behaves in a similar fashion, decreasing early but returning to control values later during the stable phase of the hypotensive reaction. Likewise, blood flow in the limbs is essentially unchanged during the hypotensive response to *V. viride.* Although blood flow through the brain has not yet been measured, clinical impressions of the patient's sensorium and ophthalmoscopic observations of the eyegrounds suggest that these areas receive adequate circulation during the hypotension."

The effects of *V. viride* have been observed in two small groups of patients treated (with Vertavis or Veriloid) for a number of months. The drugs were at best palliative, not curative. The hypotensive effects during continuous treatment were considerably less than those on initial trial.

As judged by the average arterial pressures, 80 per cent of the patients treated were improved. "Thus, on Vertavis 11 per cent of 34 patients followed for 1 to 13 months had a lowering of 50 mm. or more, and 70 per cent a lowering of 20 or more in average systolic pressure, and 14 per cent had a decrease of 30 or more, and 41 per cent a decrease of 20 or more in average diastolic pressure. Similarly, in 20 patients followed for 6 to 20 weeks on Veriloid the average systolic pressure showed a reduction of 50 mm. or more in 30 per cent and 20 or more in 70 per cent, and the diastolic a lowering of 30 or more in 30 per cent and 20 or more in 70 per cent. In both groups, only rarely was the arterial pressure restored to normal, and in these cases the pressure initially had not been excessively high. Rather, the

characteristic effect of the drug was to moderate, not to eliminate, the hypertension.

"Associated symptoms and signs of hypertension in general have been favorably affected or at least have remained unchanged in patients whose arterial pressures have been lowered during continuous treatment with *V. viride*. Similar observations have been reported after a number of other measures, which have successfully reduced the arterial pressure in hypertensive patients for prolonged periods. Thus, in favorable cases, cardiac enlargement, with or without frank congestive failure, has decreased, competence has increased, and electrocardiographic abnormalities have improved after Veratrum therapy. Retinopathy has decreased, in some cases in a startling fashion. Renal function, except in certain cases of chronic nitrogen retention that progressed during therapy, has remained adequate. Only 4 patients have had signs of cerebrovascular accidents while on the drug, and in only 1 of these was it possibly due to a hypotensive reaction to the drug.

"On continued administration there have been no evidences of development of tolerance or idiosyncrasy to the drug. Unfortunately, on long term treatment almost all patients have experienced more or less nausea and vomiting, and a few have had collapse reactions similar in every way to those following acute overdosage. In part, this undoubtedly is due to the critical dosage requirements of the drug. . . . In part, it seems also to be due to the fact that patients on continuous oral treatment, especially with Veriloid, apparently become more reactive to the same doses of the drug, and require a reduction of dosage after several weeks of therapy, to avoid nausea and vomiting or excessive hypotensive reactions, or both. Finally, there is a question whether some of the nausea and vomiting may be a central nervous system effect indissolubly associated with acute systemic hypotension, since similar symptoms occur from comparable hypotensive responses whether to spinal anesthesia, pyrogens or sympatholytic drugs. Whatever the mechanism; this annoying side effect of the drug has continued to be the chief deterrent to its continuous use in dosage adequate to produce sizable hypotensive effects."

"The dosage of *V. viride* in the chronic treatment of hypertension is extremely critical. Thus, little or no effect may occur after a certain dose when an increase of 10 to 20 per cent above that dose may cause definite or even profound effects. This is an unfortunate characteristic of the drug from the practical point of view, since it necessitates the greatest of care on the part of both patient and physician to establish a symptom free therapeutic dosage schedule. Moreover, the dosage requirements may vary considerably from patient to patient, so that only by cautious trial of increasing doses can the proper schedule be established for a given patient."

It has been found that the most satisfactory mode of administration is by mouth, four or more times a day. "This is because the drug is apparently eliminated slowly, so that to obtain a continuous smooth effect, overlapping of dosage is required. Thus, on continuous administration the action of the drug begins to appear about half an hour after a dose, reaches its peak at about two hours and diminishes over the next five to eight hours. By administration every three to five hours in smaller than therapeutic doses, an effective level of the drug may be established without producing peaks that may cause nausea, vomiting or excessive hypotension.

"The drug is better tolerated after meals and at bedtime, confirming clinically the experimental observations in animals and man that it is less nauseating when taken on a full stomach or while the patient is lying down, or both. On the other hand, eating at the peak of the drug's activity may induce nausea and vomiting, which otherwise would not occur. Therefore, it has seemed wiser not to administer the drug oftener than every two hours nor to eat within three hours after taking it. Preliminary trial of Dramamine (50 mg. before each meal) for relief of nausea, has apparently given aid in a few patients, but none in others.

"All the preparations of *V. viride* so far available have produced more or less nausea and vomiting, and it seems fair to say that this has been the chief objectionable feature of the drug. . . . There have

cc. was used in 366 injections and 2.0 cc. in 649. In the other six injections, intermediate amounts were given. The initial dose was usually 1.0 cc. Smaller doses than this were given when sensitivity to mercury was suspected. In 1 patient, 1.0 cc. proved to be too large and 0.5 cc. was given subsequently."

"Most patients received injections on a biweekly or weekly schedule. In 9 patients, daily injections were given, although this is not usually recommended. On the daily schedule, however, few received more than six injections. One individual was given 2.0 cc. of the drug daily for 16 days, without experiencing untoward effects. Excellent diuresis resulted in a weight loss of 9.0 Kg. The largest number of patients received from 6 to 10 Thiomerin injections; 5 received more than 31, and 2 more than 50."

Dyspnea, orthopnea, pulmonary edema and massive anasarca were present in a 78 year old man suffering from congestive failure. "He was digitalized on admission and placed on a 3.0 Gm. salt diet. Nine injections of Thiomerin were given over a 21 day period. Excellent diuresis resulted in a weight loss of 16.0 Kg. Because of the patient's difficulty in voiding, an indwelling catheter was maintained in place during the period of these observations. The collection and measurement of urinary output were therefore accurate.

"The diuretic effect of Thiomerin was compared with that of Mercuzanthin in similar dosages in 54 patients and with that of Mercuhydrin in 22, regarding loss in weight or diuresis or both. In 5 patients the latter was possible. One significant difference between Thiomerin and the other two drugs was observed in 67 of these patients. Thiomerin resulted in a more even and more prolonged diuresis, which usually began 12 to 18 hours after the injection and might continue for 48 hours. In 11 patients, Thiomerin was superior to either of the older mercurials. Five of these patients had received Mercuhydrin before Thiomerin was given, 5 Mercuzanthin and 1 had been given both drugs. Its superiority was manifested by more marked diuresis with greater loss of weight and by subsequent clinical improvement. As a result, Thiomerin could be given to these patients either less frequently or in smaller amounts than had been possible with the other mercurial drugs.

"Thiomerin was substituted for Mercuzanthin and Mercuhydrin in 3 patients because of sensitivity reactions to these drugs. In 1 of these 3 patients a rash and fever followed on each occasion that Mercuhydrin was given. Mercuzanthin in 2.0 cc. amounts given intravenously had become relatively ineffectual. The patient suffered from severe congestive failure and massive anasarca was present. One cubic centimeter of Thiomerin was given subcutaneously on 6 occasions over a seven day period. Diuresis was marked, resulting in a weight loss of 9.9 Kg. Five more injections over a 10 day period resulted in a further loss of 6.6 Kg. in weight with dramatic clinical improvement. Untoward reactions to Thiomerin have not appeared in this patient. Since then, she has received more than 50 injections. . . . The second patient developed an urticarial reaction to Mercuhydrin and the third, the same type of reaction to Mercuzanthin. Thiomerin has been effective as a diuretic in both of these patients without sensitivity reaction.

"The diuretic effect of Thiomerin did not seem inferior to the effects of the other mercurial drug to which it was compared in any patient. In 22 patients an opportunity for comparison with the other mercurial drugs was not possible as only a few injections of Thiomerin were required to effect adequate diuresis, after which diuretics were no longer required.

"Two patients received the drug intravenously subsequent to its use by the subcutaneous route. In them the total diuretic effect was approximately the same as by the subcutaneous route, although the onset of diuresis was more rapid and its duration less prolonged.

"An estimate of the effect of Thiomerin on the body weight was possible in 89 patients. Loss of weight occurred in 47. The weight remained stable in 41 subjects. Only 1 patient in the whole series gained weight due to fluid accumulation while receiving Thiomerin in adequate dosage and frequency. This subject was a 44 year old alcoholic suffering from cirrhosis of

the liver. Ascites was increasing. No better effect resulted from Mercuhydrin than from Thiomerin in similar amounts.

"Eighty-six patients were on maintenance amounts of digitalis; 26 were also receiving ammonium chloride. In 7 patients when ammonium chloride was discontinued temporarily, slight but definite decreases in diuresis and gains in weight were recorded."

As for reactions to Thiomerin, temporary local pain or tenderness was the most common complaint. "It occurred occasionally in 42 patients. The discomfort usually lasted from one minute to one hour and was described as varying from mild to moderate in intensity. In rare instances it was described as having a burning quality. Discomfort was accompanied in 4 patients by local ecchymosis which subsequently cleared entirely and did not prevent the continued use of the drug. In 6 other patients, moderately tender nodules appeared occasionally at the sites of injection. These were slowly reabsorbed over a 7 to 10 day period. In 1 patient they appeared more frequently and were more persistent. For this reason the drug was subseqently given by the intravenous route without untoward reaction. These reactions have not occurred with later batches of the drug.

"Cramps in the calves of the legs were recorded in 3 patients when the diuresis was perhaps too large and too rapid. When either the dose of the drug or the frequency of injections was reduced these symptoms did not occur.

"A superficial slough occurred in the skin in 1 patient. This untoward result followed the ninth injection the patient had received. It was given superficially and quite likely, in part, intradermally. The use of the drug was subsequently continued in this patient, with precautions taken for subcutaneous administration, and the area of superficial slough healed without further untoward reactions. This reaction was attributed to the drug being given too superficially.

"Reactions were not observed in 58 patients."

Thiomerin appears to be the drug of first choice at the present time for most patients requiring mercurial diuretics.

Studies on Thiomerin. A Subcutaneously Administrable Mercurial Diuretic — Grossman, J., Weston, R. E., Edelman, I. S. and Leiter, L. — *Circulation*, 1: 508 (April, Part I) 1950.

In this study, Thiomerin, a subcutaneously administrable mercurial diuretic, was used in the treatment of chronic congestive cardiac failure.

"The subjects were 21 hospitalized patients and 12 outpatients, most of whom were in well established chronic congestive cardiac failure of varying etiologies. Of these, the etiology was rheumatic fever in 11, hypertension in 7, coronary arteriosclerosis in 11, combined congenital anomaly and hypertension in 1, and cor pulmonale in 1 patient. Two patients had localized edema; in 1 due to immobilization and in the other to an unknown cause. Despite the relatively advanced state of their illnesses, marked peripheral edema was uncommon, owing largely to a well controlled, low sodium intake of less than 800 mg. daily. Under this dietary regimen, the need for mercurial diuretics fell sharply."

In general, therapy other than mercurial diuretics was not influenced by this study. "Digitalis and quinidine were given as indicated; ambulation was encouraged when the patient's condition permitted it. Ammonium chloride was not given since chloruresis was utilized as a measure of response. To limit the number of variables, adjuvant therapy such as aminophylline was avoided. Mercurials were administered in terms of the patients' needs and by the following routes: Thiomerin generally subcutaneously, Mercuzanthin intravenously, and Mercuhydrin (methoxy-oxymercuripropyl-succinylurea) intramuscularly. The dosage of any mercurial never exceeded 2 cc., which is equivalent to 80.0 mg. of mercury; occasionally smaller amounts were used. More than 300 injections have been given."

"In most patients, the 24 hour urinary volume after subcutaneous injection of Thiomerin increased 1,000 to 1,500 cc. above control levels. At the same time, there was an approximately tenfold increase in chloride excretion which, in these patients on low salt intake, averaged 0.2

to 0.3 Gm. (5.6 to 8.5 mEq.) per 24 hours, during control periods. However, the responses in individual patients varied." In 1 patient whose daily urine volume and chloride output rarely exceeded 1,000 cc. and 0.3 Gm., respectively, urine volume increased to 4,000 cc. with an associated chloride excretion of 12 to 15 Gm. On the other hand, in another patient whose response to mercurials was reduced, increased chloride excretion occurred despite little or no increase in urinary volume.

Of special significance was the comparison between the effects of Thiomerin and other mercurials in the same patient at approximately the same weight. The data indicated that the diuretic effect of Thiomerin is not significantly different from that of other mercurials, including failure of response in some patients.

The typical effects of intravenous Thiomerin on renal hemodynamics, water, sodium and chloride excretion, and uric acid clearance in a noncardiac patient were observed. "The sequence of events is as follows: During the first 30 to 40 minutes after injection, no diuretic response is evident. Then, urine output and sodium and chloride excretion increase rapidly, reach a maximum at 60 to 70 minutes, and gradually decrease thereafter. As a rule, the changes in water and electrolyte excretion occur simultaneously. When electrolyte output exceeds one tenth of a milliequivalent per minute, the excretions of sodium and chloride tend to rise and fall to an equal degree so that the two curves of excretion virtually coincide. Generally, no significant change in glomerular filtration rate or renal plasma flow occurs during the two to three hour period of observation following Thiomerin administration."

Data on renal hemodynamics and water and electrolyte excretion before mercurial administration and during the period of maximal diuretic effect was obtained. "Generally, maximal increase in electrolyte and water output occurred together, but in 3 cases, maximal water diuresis occurred earlier."

The close correspondence between sodium and chloride excretion in these experiments was striking. "In the noncardiac patients the time of maximal response on intravenous injection was fairly constant and occurred earlier than in the patients with congestive failure."

The chief difference between subcutaneous and intravenous routes of administration is the occurrence of diuresis 30 to 50 minutes earlier on intravenous administration. In 1 patient there seemed to be a more abrupt, somewhat greater, but less sustained rise of diuresis on intravenous administration than on subcutaneous injection. In 2 other patients, however, there was little difference in the height of maximal response between the two routes of administration.

"Uric acid excretion was measured in 8 patients prior to and following administration of Thiomerin and Mercuzanthin." There was a distinct rise and fall in uric acid excretion after both Thiomerin and Mercuzanthin administration. "Since no rise in the glomerular filtration rate or plasma concentration of uric acid occurs, the increase in uric acid clearance probably is due to increased tubular reabsorption." The maximal mercurial effect on uric acid excretion occurs long before that on water and electrolyte excretion. "This difference may be due to greater sensitivity of the uric acid tubular transport mechanism to the action of mercurials.

"In 4 patients, electrocardiograms recorded during the intravenous injection of Thiomerin revealed no changes attributable to the injection. Similarly, the examination of the urine of several patients who had had repeated injections of Thiomerin revealed no changes from the pretreatment findings, although certain thiols or their mercury complexes have been said to produce hematuria. Apparently, a therapeutic dose, given twice weekly for four to six weeks, does not produce clinically demonstrable renal damage.

"Subcutaneous injections of Thiomerin produce no more pain than does any subcutaneous aqueous injection. In more than 300 injections, no systemic reactions of any severity occurred. Two severe local reactions were encountered. The first followed the injection of 2 cc. of Thiomerin into a dependent, grossly edematous area of the thigh, and consisted of pain, redness, and ulceration. The effects were attributed to poor absorption of the injected material. The second occurred in a patient known

to have a hemorrhagic diathesis, and consisted of a large area of ecchymosis which extended from the upper arm to the shoulder and elbow, with subsequent discoloration. It was accompanied by pain, induration and limitation of motion, but good diuresis. Both patients received Thiomerin subsequently without ill effect. The only other reactions observed were small subcutaneous nodules at the site of injection in some patients who had had repeated injections. In all but 2 instances, these were painless."

Thiomerin, like other mercurials, acts by decreasing tubular activity.

Early Pregnancy Diagnosis with the Reaction of Galli Mainini. Considerations on Its Application — INCLAN SANDOVAL, AURELIO — *Revista cubana de laboratorio clinico*, 4: 62 (April-May-June) 1950.

The author reports on more than 1,000 pregnancy tests carried out with male Batrachia occurring in Cuba. The tests are based on the fact that the chorionic gonadotropin present in urine of pregnant women acts directly on Sertoli's cells of the testicles of Batrachia and causes in them a series of modifications with the result of detachment of the spermatozoids which are encountered free in the lumen of the seminiferous ducts and which then pass through canaliculi and through a mesentery, linking testicle and kidney and are then excreted together with the urine.

Male frogs (Catesbeiana of Shaw) and male toads (Bufo peltacephalus) have been used with good results. The statistics refer to frogs as they are easy to obtain; they are captured at night when they are out to feed. The frog Catesbeiana of Shaw has continuous spermatogenesis; its mature spermatozoids are encountered in its testicle throughout the year, while other frog species have a cyclic spermatogenesis with periods of sexual activity and rest. When a lot of frogs is received at the laboratory the females must first be eliminated; the author has found two infallible and easily observed characteristics; namely, that the males always have a greater ear drum, and that they always have at the level of the ventral wall and around the mouth, in the region of the guttural sacs a yellow color which is regularly visible even in speckled and dark individuals and which is never present in females; some males show an intense canary yellow color in this area. Males from 70 Gm. on have been used with good results. The animals are kept in rectangular pools with a fixed water level and with a declining floor so that the animals may stay in the wet or in the dry part; in this manner death from immersion and infections are avoided. They are fed water cress and probably catch insects at night as when in liberty. In this manner the animals may be kept for up to five months. Ulceration has been observed at the place of injection of the urine, after repeated injections, but this does not interfere with the test unless the urine drains out again after injection.

Three animals are used for each test. With a 1 cc. pipet introduced into the cloaca several drops of urine are withdrawn and if microscopically no spermatozoids are found in this urine the animal is suitable for the test. Then the urine is injected into the ventral wall in an anteroposterior direction at the side of the sternum; 15 cc. of urine are used if its specific gravity is below 1.010, 13 cc. if it ranges between 1.010 and 1.025, and 8 cc. if it exceeds 1.025. The animals are placed in a cage with three compartments, and urine is taken again from each of them after one and two hours. If spermatozoids are encountered in the urine of any of the animals, the test is positive. Three animals should be used as frequently, only 2, and sometimes only 1 of them will furnish a positive result. It was at first believed that animals which did not react positively in a positive case did so for sexual causes, but it has been shown that they may react well in other cases; the concentration of the urinary chorionic gonadotropin is largely responsible for the differences in reaction. However, animals which have been used more than six times and which have lived for a long time in captivity will show considerable diminution of their usefulness without long rest periods, and are liable to succumb to the test.

The injection is made high up at the level of the sternum as in this manner the urine will not drain out through the needle hole with the animal in its habitual position. A larger amount of urine of low specific gravity is used as it has a lower

gonadotropin concentration, and as concentrated urine is more difficult to absorb and more toxic. The urinary *p*H is of no importance. Cloudy urine with precipitation particularly of ammonium-magnesium phosphate is filtered before injection as otherwise absorption is impaired possibly due to clogging of the lymphatics by the crystals. Morning urine is used, but this selection is not indispensable. Urine kept in the refrigerator for five days has been used with good results. Drugs present in the urine, and treatment of the patient with estrogens, progesterone and gonadotropin do not interfere with the results of the test. The test was positive after one hour in 60 per cent, and after two hours in 100 per cent. Quantity and mobility of the spermatozoids encountered in the urine need not be taken into consideration in reading the results; in 90 per cent of the cases the latter may be done macroscopically on the basis of cloudiness of the urine, but microscopic examination is done routinely. Inexperienced observers may confuse flagellates with spermatozoids; such infestation was found in 60 per cent of the animals, and in such cases the urine will be stained yellow by feces as these animals have a single orifice for urine, feces and sexual secretions. Animals which have been positive may be used again after their urine has become free of spermatozoids; they may turn negative after 36 hours to 4 days and may be used again after 10 days. Animals which have been negative may be used again immediately, but a rest of 4 days is given them after a second negative injection. Instead of the urine, 2 cc. of serum may be used for the injection with the same technic otherwise. On cold days, which are rare in Cuba, the cage is placed on an electric water bath of 56°C. so that the vapor warms the animals without dehydrating them, in order to obtain the results more rapidly.

In hospital practice use of 3 animals is difficult and a control test is used in the following manner: Animals reacting negatively are injected with a definitely positive urine and if they react positively the original test is considered negative, while animals reacting negatively repeatedly are discarded.

The positive results were correct in 100 per cent of 546 cases, and the negative results were correct in 677 out of 683 cases, or 99.12 per cent. The amenorrhea in the positive cases had lasted 4 days in 6, up to 10 days in 196, up to 2 weeks in 287, up to a month in 51, and longer in 6 cases. In ectopic pregnancies the positive result was correct in all 22 cases, and the negative in 24 out of 26 cases. Correct positive results have been obtained in 2 cases of chorionepithelioma and 8 of hydatidiform mole. In 12 cases of threatening abortion the results were correct. In 6 cases of incomplete and 9 of complete abortion the results were positive, turning negative after a week. A comparison with the Friedman-Brouha test showed that the positive Mainini test is more reliable than the positive Friedman-Brouha test, while the negative Friedman-Brouha test is more reliable than the negative Mainini test.

The author concludes that the Mainini test is simple, economical and reliable but that the proper technic and precautions are important.

The Two-Step Exercise Electrocardiogram. A Test for Coronary Insufficiency — MASTER, ARTHUR M. — *Annals of Internal Medicine*, 32: 842 (May) 1950.

"Diagnosis of heart disease is often complicated by the fact that objective evidence of organic disease cannot be obtained. In many cases of coronary disease with angina pectoris, physical examination, roentgenographic representation of the size of the heart and cardiac pulsations, and electrocardiogram are normal. Patients with valvular disease often complain of symptoms such as dyspnea and pain when physical examination fails to reveal evidence of heart failure."

"In cases of this type, a functional test, that is a test which obtains the response of the heart to effort, may be of great value in diagnosis and in evaluation of functional capacity. The '2-step' exercise test, which was devised to provide such a test, has proved to be a reliable method of measuring cardiovascular function.

"In addition to its value as a diagnostic aid in cardiac disease, the '2-step' exercise electrocardiogram test has proved useful in following improvement of patients dur-

ing convalescence. It is a valuable aid also in the field of investigation."

"The '2-step' exercise test is a simple procedure. It consists of ascending and descending two 9 inch steps a variable number of times (depending on age and weight) in one and one-half minutes. The accustomed nature of the work allays apprehension or excitement, thereby reducing psychic disturbance to a minimum. Even in these days of elevators, stair climbing is so routine a type of work for everyone that it does not arouse mental reactions which, by increasing blood pressure and pulse rate, or which, by affecting the coronary circulation, may influence the very factors utilized in estimating the circulatory response to exercise. Since the '2-step' exercise is a sufficient test of cardiac function, as well as a natural type of effort, it may well replace tests which subject the patient to unnatural and excessive physical strain.

"Numerous investigators have pointed out that excessive exertion causes electrocardiographic changes in normal persons. . . . Apparently it is not usually recognized that when a patient is required to make unusual or excessive effort, the psychic, mental and physical reactions are unduly strong and consequently blood pressure, pulse rate, and electrocardiographic reactions are too pronounced to permit accurate estimation of cardiac function. Similarly; if the effort exerted is too slight, the electrocardiogram of even a person with coronary sclerosis may fail to register deviations from normal.

"If exertion is to be measured accurately, the age and weight of the individual must be taken into consideration. A man weighing 200 pounds does more work climbing a step than one weighing 120 pounds, and a man who is 50 years old cannot expend as much effort as a man of 30, without undue strain." The '2-step' exercise, provides an exact measure of work performed. "Such a measure is not possible with dumbbell exercises, hopping, skipping, squatting and the like, which may be variously interpreted according to the intelligence, vigor and good will of the individual patient."

For convenience in performing the test a simple "two-step" contrivance was constructed of ¾ inch wood, with two steps on each side. "Each step is exactly 9 inches high and from 22 to 27 inches wide. The appearance of the apparatus does not cause foreboding, and the steps can be utilized as a seat or a shelf or placed out of the way under a table when not in use."

"Adequacy of the coronary circulation is revealed in the exercise electrocardiogram. Normal persons usually show no deviation following the exercise. Positive changes in the electrocardiogram (RS-T depressions, changes in the direction of the T waves, and the like) are indications of coronary insufficiency. That the electrocardiographic changes following exercise are correlated with the oxygen supply of the heart muscle is shown by the fact that inhalation of mixtures of 10 per cent oxygen for 20 minutes may produce similar changes in the electrocardiogram. Exercise produces an oxygen debt."

"The procedure for obtaining electrocardiographic records in the '2-step' test is as follows: The electrodes are attached to the patient and his weight is recorded. He is then requested to sit down in a reclining chair or to lie on the examination table and to make himself comfortable." The number of times that he is to climb the "steps" is determined from a standard table. "Next the electrocardiogram is taken. The technician or physician then demonstrates the procedure by climbing over the steps two or three times. The patient at a given command walks up one side of the steps and down the other, always turning to the same wall or side of the room before each ascent to prevent vertigo. He makes a trip only when he receives the count and the required number of ascents is completed in one and one-half minutes. If the patient climbs too slowly he is told to move more rapidly, if too fast, his ascents are made more deliberate. A stop watch, a wrist watch or electric clock with a sweep hand is used. At cessation of the exercise the patient sits down and the four leads of the electrocardiogram are recorded immediately. The electrocardiogram is then recorded at two and six minutes after cessation of exercise. Only a few beats in each lead are necessary.

"Certain extracardiac factors which may influence the electrocardiogram must be taken into account. Some drugs, such as

thyroid extract and ephedrine affect the exercise tolerance. Alcoholic intoxicants or excessive smoking may have a similar effect. Distention of the stomach following a meal impairs the movements of the diaphragm; therefore the test should not be performed for at least one hour after a meal. An acute upper respiratory infection may be reflected in the electrocardiogram. Perhaps more important than any of the factors just mentioned are the changes induced in the electrocardiogram by intense excitement or emotion. (Slight excitement, emotion, or nervousness will not affect the results.) An attempt therefore should be made to put the patient at ease. The 'resting' electrocardiogram may be taken in either a sitting or a lying position, provided the patient returns to the same position after exercise. The room in which the test is performed should be neither too quiet, nor too noisy; rather there should be an atmosphere of reassurance and of ordinary life. The patient is shown how to do the test for two or three trips. He is assured that the test is entirely harmless but that if he develops any untoward symptoms he may stop. Pain or shortness of breath are very seldom engendered by the test. A man who cannot walk 50 feet out-of-doors without stopping because of chest pressure, will have no symptoms during or following the '2-step' exertion, except on the rarest occasions. It may be that walking outdoors, or climbing a flight of stairs produces a sort of conditioned reflex, but patients who cannot take such exercise without discomfort, perform the '2-step' exercise with relative ease and equanimity.

"In interpretation of the electrocardiogram, the P-R interval is taken as the control level. Depression of the RS-T segment of over 0.5 mm. in any lead is considered a positive result. In other words, the level of the string just following the QRS complex, is compared with that immediately preceding the complex."

"A change from an upright T wave to an isoelectric (flat) or inverted T wave is also an abnormal response; so, too, is a change in the other direction; that is, from a flat or negative, to a positive T wave. Occasionally, premature beats or some more significant arrhythmia, widening of the QRS, intraventricular or bundle branch block, large Q waves, prolongation of the P-R interval, or heart block may appear. All of these are considered abnormal responses to the exercise. A change from an inverted or flat T wave to an upright T wave is abnormal. Although this may appear paradoxical, clinical experience has proved that such a reaction is not normal. The same type of change has been seen during the 10 per cent anoxemia test. For example, in the electrocardiogram of a patient with coronary disease a T_1 that is inverted before the test, becomes upright as the patient becomes anoxemic, even cyanotic, with chest pain.

"A change from an inverted T wave to an upright wave in lead III alone is not a positive result since this is frequently observed in normal persons. (Perhaps it is because the diaphragm becomes depressed during or shortly following exertion.)"

A follow-up of many patients confirmed the accuracy of the electrocardiographic findings in the "2-step" test.

Orchitis in the Course of Severe Chickenpox with Pneumonitis, Followed by Testicular Atrophy — WESSELHOEFT, CONRAD AND PEARSON, C. M.— *New England Journal of Medicine*, 242: 651 (April 27) 1950.

"A case of severe chickenpox in an adult with a severe virus type of pneumonia, unilateral orchitis and epididymitis, with subsequent testicular atrophy, is reported. Only 1 other case of orchitis during the course of chickenpox has been found in the literature."

"In the following case a unilateral orchitis and epididymitis occurred in conjunction with miliary pneumonia; partial atrophy of the testicle followed—a condition that is here reported for the first time."

Case Report.—A 46 year old salesman was admitted to the writers' hospital on December 11, 1948, with a diagnosis of chickenpox. "The patient had never had any of the common childhood diseases except scarlet fever. The chickenpox eruption had first appeared four days prior to admission. Seventeen days before the onset he had been exposed to the disease by his own children.

"Physical examination showed a very extensive and very typical eruption on the face, body, extremities and in the axillas with a few characteristic superficial vesicles on the palms and soles. The lesions were pleomorphic, presenting both the vesicular and scab forms. The corona or erythematous base of each lesion presented a dusky, cyanotic hue, as did the lips and finger nails. There were broken vesicles on the soft palate and a multilocular vesicle on one tonsil. The reason for hospitalization was extreme respiratory distress with cyanosis of 18 hours' duration. The respiration varied between 30 and 40 per minute and was interrupted by periods of incessant coughing. Fine, crepitant rales were present throughout the chest. The heart rate varied with the respiratory distress between 128 and 100 per minute. The patient complained of nausea but did not vomit, was extremely restless and apprehensive and at times was disoriented. Immediately after admission he was placed in an oxygen tent. He was also given 40,000 units of penicillin every three hours and 250 mg. of streptomycin every six hours. Demerol and paraldehyde were used for the extreme restlessness.

"The urine was amber in color, with a *p*H of 5.0 and specific gravity of 1.028, and gave negative tests for albumin, sugar and bile and a +++ test for ketones; the sediment contained many white cells, no red cells and many granular casts.

"Examination of the blood revealed a hemoglobin of 16 Gm. and a white cell count of 10,400, with 60 per cent neutrophils and 40 per cent lymphocytes. The sedimentation rate was 3 mm. in one hour. The blood Hinton reaction was negative. A test for cold agglutinins was negative on December 24.

"A throat smear disclosed many gram-positive and gram-negative bacilli and cocci. A throat culture grew alpha-hemolytic streptococci (++++) and *Staphylococcus albus* (++), with the same organisms in the sputum.

"A blood culture was negative in eight days.

"Subsequently, urinalyses showed a few transient red cells in the sediment, and examinations of the blood demonstrated a rise in the white cell count to 14,800 with 82 per cent neutrophils.

"X-ray films of the chest revealed a characteristic extensive miliary pneumonia of the viral type throughout both lung fields. An electrocardiogram taken on the tenth day was within normal limits.

"During the first five days in the hospital the respiratory symptoms showed a slow progressive improvement. The temperature varied between 100 and 102° F. By the fifth day all signs of mental confusion had disappeared, and the patient was taking fluids well. The skin lesions, as one frequently observes in severe forms of the disease, showed marked variation in development, some shifting rapidly into scabs and others remaining in the vesicular state for a few days and their contents changing from clear fluid to a milky consistence. These variations were still present five days after admission and nine days after the onset of the illness.

"On that day (December 16) the patient first complained of pain in the right testicle, which was found to be swollen and tender, with enlargement of the epididymis. The temperature rose to 102° F., without a chill or chilliness." Judging from their experience with mumps, the writers should have classified this case as a mild or moderate orchitis, for the testicle never became hard, was only a little more than double its original size and at no time was seriously painful. "A rectal examination revealed a normal prostate. At the end of one week the testicle and epididymis had returned to normal.

"Except for a severe diarrhea with bloody stools on December 18 and a dermatitis medicamentosa on December 20, there was continuous and steady improvement. The patient was discharged on December 26 after five days of normal temperature.

"He returned to the hospital on January 10, 1949, for follow-up study. A few subcrepitant rales were still present on deep breathing, and an x-ray film showed marked clearing but the miliary process was still in evidence. The testicles were normal. He had gained back much of his strength and weight and was no longer coughing. A final return visit was made on June 27, six and one-fourth months after the onset of the illness. In the interim he had remained well. He had worked steadily at his job as a salesman. Physical examination at this time was entirely negative

except for the right testicle, which was found to be a third smaller, of a softer texture, more irregular and somewhat less sensitive than the normal left testicle. The right epididymis was normal. An x-ray examination of the chest and blood studies were entirely negative."

"As was to be expected, the administration of penicillin and streptomycin in this case was ineffective against the virus of chickenpox. These antibiotic agents were given to prevent secondary bacterial invasion of the pneumonic process."

Q Fever in a Wool and Hair-Processing Plant — Sigel, M. Michael, Scott, T. F. McNair, Henle, Werner and Janton, O. Henry—*American Journal of Public Health*, 40: 524 (May) 1950.

"An outbreak of Q fever occurred in Philadelphia among workers in a wool-processing plant."

It was established that during the first three months of 1948, about 30 employees of this company had been away from work because of a respiratory illness generally called "flu" or "grippe."

"A visit was made by the authors to the wool-processing plant and, following a conference with the manager, permission was secured to bleed all employees. Between the last week of June and the second week of July, 152 of the 186 employees were bled and their serums were tested with the antigen of Q fever. Sixty-seven of these serums gave positive reactions ranging in titer from 1:2 to 1:2,048; 39 of the serums had titers of 1:64 or higher. This was considered as indirect evidence that a large number of the employees had had contact with *Coxiella burneti*." Observations suggested that the outbreak of illness in this plant in the winter of 1948 was due to the rickettsia of Q fever.

"The plant is engaged in the processing of wool and goat hair. Raw and scoured wool is imported by the company from many countries, and wool imported by several other companies is also processed in this plant. The plant itself is subdivided into six departments: office, warehouse, blending, scouring, dyeing, and maintenance. The scouring is done at a temperature of over 200° F. for 15 to 20 minutes, which will presumably kill *C. burneti*. The office is separated from the actual plant by the warehouse and by a loading ramp. Most of the employees are males, since only 3 women are employed who work in the office. Among the 152 employees tested in this study, there were 91 Negroes and 61 whites.

"The important findings noted during visits were:

"1. Not all wool was scoured.

"2. The plant operations produced great amounts of dust."

"The technique for the complement fixation test was as follows: Serially diluted serum in 0.1 ml. amounts was mixed with 0.1 ml. of suitably diluted antigen and 0.2 ml. of complement containing approximately 1.5 units, as determined by preliminary titration in the presence of antigen. The tubes were kept in the refrigerator for approximately 18 hours. After this time, to each tube was added 0.2 ml. of sensitized sheep red cells (2 per cent cells with an equal amount of amboceptor in dilution considered optimal by titration of serial dilution of amboceptor with serial dilutions of complement), and the tubes were incubated at 37° C. for 30 minutes. The highest dilution of serum giving a 3+ or 4+ reading was considered the end point. The initial dilutions of serum (before the addition of the other reagents) were used to express the titers. All serums were first tested in low dilutions with the antigen of Q fever. Serums which reacted in the preliminary test, and some of those giving negative results, were subjected to quantitative complement fixation tests using several antigens. These included the Q fever antigen, influenza A and B soluble antigens, and the lygranum antigen. A few were also tested with the antigen of epidemic typhus." A number of serums were also tested by the Kolmer test technique for syphilitic antibodies.

Among the 37 individuals classified as having been ill, there were 30 whose serums reacted with the antigen of Q fever, whereas among the 115 reporting no illness, there were 35 whose blood contained antibodies to this antigen. "The presence in the second group of a substantial number of serums with antibodies to *C. burneti* suggested that a number of workers had inapparent infections or illness of such

mild character that they did not remember it."

In regard to the significance of titers to *C. burneti* in single serum specimens, the authors feel that titers of 1:128 and higher are certainly diagnostic. "A titer of 1:64 or 1:32 may also be indicative of recent infection, while titers of 1:8 to 1:16 are considered of doubtful diagnostic significance and may actually represent infection in the past. Titers of less than 1:8 are considered insignificant."

Owing to the paucity of clinical records on the individuals involved in this outbreak of Q fever, the clinical data are incomplete and not always reliable. "In general, the illness was very mild, and the workers believed they had colds or 'flu.' Only 2 workers were hospitalized and a small number were seen by physicians. Only one physician remembered one of the patients as presenting a bizarre clinical picture which, according to the doctor, did not quite fit the usual course of influenza or grippe. . . . The other patient was treated at another hospital, where he was admitted on March 5, 1948, and discharged on April 10, 1948. The diagnosis of his illness was 'lobar pneumonia.' This patient, whose pneumonia was complicated by pleural effusion, had fever, dyspnea, and slight cyanosis. Pneumococci were found in the pleural fluid on March 31, 1948. The severe pneumonia in this individual may have been a secondary infection superimposed on the Q fever."

"All men admitting to illness were questioned and their symptoms and signs tabulated." These are shown in the following chart:

Signs and Symptoms as Related by 28 Workers

Fever	21
Sweats	21
Chills	20
Generalized aching	18
Sudden onset	16
Headache	12
Cough	9
Anorexia	9
Sore throat	6
Chest pain or discomfort	4
Diarrhea	3
Bloody sputum	0
Abdominal pain	0
Constipation	0
Epistaxis	0

The most prominent symptoms; i.e., feverishness, sweats, chills, and malaise reported by this group were the same as those described as most common in other outbreaks.

Although the first patient complained of a severe headache, and though reports of other outbreaks listed headache as one of the most prominent symptoms, only 12 of the workers said they had had a headache.

"According to the statements received during the interviews, the average number of days of illness was approximately 14 for the patients with Q fever. This figure is higher than the average reported by other investigators and probably represented the time of illness plus convalescence; i.e., absence from work rather than the period of fever. Patients showing no serologic evidence of this disease had illnesses of approximately two days. The disease was rather mild and . . . . there appeared to have been at least 8 individuals with inapparent illness. Possibly all 22 workers with a titer of 1:32 or higher in the nonill group might have had inapparent infections. There was no correlation between the frequency or severity of illness and the age of the workers."

"The interviews of the employees at this plant revealed that 9 were ill in January, 14 in February, and 5 in March. One worker who was employed on December 31, 1947, and another who started early in January had Q fever. This indicates that *C. burneti* was present at this plant after December 31, 1947."

"The highest incidence occurred in the dyeing and warehouse departments and among the mechanics. . . . Raw wool was handled in the warehouse, dye house, blending and scouring departments. Furthermore, a large amount of dust prevailed throughout the plant, which might explain the presence of disease in all departments except in the office which was separated from the rest, since particles bearing the rickettsiae might have been present in all the working sections of the plant."

"It appears that this outbreak was caused by *C. burneti* inhaled by workers handling raw wool and goat hair—presumably containing dried ticks or tick feces—in a dusty atmosphere. . . . There

were no known cases among the contacts or families of the workers."

"Q fever should be recognized as an occupational hazard. The disease has now been shown to occur among stock handlers, packing house workers, and workers in the wool industry. In addition, it may be transmitted to consumers by milk." The authors feel that the public health authorities, federal, state, and local, should take the necessary steps to make Q fever a reportable disease, and to extend the protection and benefits of the laws covering compensation to include Q fever.

"From the standpoint of prevention of Q fever in the wool industry, several prophylactic and control measures may be mentioned. Perhaps vaccination would afford protection. . . . Every effort should be made to reduce materially the amount of dust produced during the various operations. A properly engineered 'air cleaning' system, supplemented by ultraviolet irradiation of 'purified' air, may lower the chances of infection. It would be most desirable that only scoured wool be imported into this country. This, however, may not be feasible owing to economic and commercial factors."

Vitamin B_{12} and Folic Acid in Megaloblastic Anaemias of Pregnancy and the Puerperium — UNGLEY, C. C. AND THOMPSON, R. B. — *British Medical Journal*, 1: 919 (April 22) 1950.

"Megaloblastic anaemia occurring in pregnancy and the puerperium is clearly distinct from addisonian pernicious anaemia with its associated gastric atrophy and permanent loss of Castle's intrinsic factor. Trials with vitamin B_{12} reported here emphasize that even the nature of the limiting haematopoietic factor may be different in the two disorders."

Six cases will be presented. "Five were classical examples of the so-called 'pernicious anaemia of pregnancy'; the sixth had unusual features. All showed megaloblastic erythropoiesis on marrow puncture.

"Case 1.—Mrs. A., aged 34, was first seen in the fourth month of her third pregnancy. She then had hypochromic anaemia with a normoblastic marrow, and received transfusions and iron. At the eight month she returned with severe swelling of the legs and vulva, and a marked anaemia, this time associated with a megaloblastic marrow. Except that she ate red meat only twice a week and disliked cabbage, the diet had been fairly good. There was free HCl in the gastric juice. Red blood cells numbered 1,530,000 per c.mm.; haemoglobin, 30 per cent (4.4 Gm. per 100 ml.); colour index, 0.98; M.C.V., 80 μ^3; M.C.H.C., 34.2 per cent; M.C.H., 27.1 $\mu\mu$g. Plasma bilirubin was 0.64 mg. per 100 ml. (direct reaction negative).

"A concentrate of Lester Smith's red pigments (not yet crystalline) was given parenterally in a dose colorimetrically equivalent to 65 μg. of vitamin B_{12}. There was no response, and after a few days the patient was transfused with blood of a group suitable for differential agglutination by the Ashby technique. Ten days after receiving vitamin B_{12} her own red blood cells had fallen to 1,130,000 per c.mm. The marrow was still megaloblastic, and oedema had increased. She was now given 2.5 mg. of folic acid daily, alternately by mouth and by injection. After four days the marrow was normoblastic. A reticulocytosis of 26.6 per cent followed, and the red blood cells increased to 2,240,000 per c.mm. in 10 days. When a yeast extract was substituted for folic acid there was no secondary reticulocytosis, and erythropoiesis continued at the same rate. The rapid rate of elimination of transfused red cells changed to normal after folic acid.

"After delivering a healthy child the patient continued to improve, red cell counts reaching normal levels without further treatment, except a course of iron.

"Case 2.—Mrs. B., aged 24, twice had megaloblastic anaemia associated with pregnancy. The anaemia which followed the birth of her first child responded to an alcoholic extract of yeast. Free HCl was present in the gastric juice. Throughout her second pregnancy she felt well, but by regular blood examination a recurrence of the anaemia was detected. At the eighth month the red blood cells numbered 3,470,000 per c.mm.; haemoglobin, 65 per cent (9.6 Gm. per 100 ml.); colour index, 0.94; M.C.V., 96.0 μ^3; M.C.H.C., 29.2 per cent; M.C.H., 27.7 $\mu\mu$g.; white blood cells, 8,900; the marrow was megaloblastic.

"An injection of 80 μg. of vitamin B_{12} did not produce a reticulocyte response,

the marrow remained megaloblastic, and in nine days the red blood cells fell to 3,190,000 per c.mm. When 20 mg. of folic acid was given daily by mouth reticulocytes rose to 4.6 per cent on the seventh day and the red blood cells increased to 3,760,000 in 17 days. After 28 days—9 days before parturition—the counts were unchanged. There was a slight fall to 3,360,000 after delivery, followed by a rapid rise to normal levels.

"Case 3.—Mrs. C., aged 32, had a routine examination at the sixth month of pregnancy which revealed an unduly low blood count; red blood cells, 2,410,000 per c.mm.; haemoglobin, 53 per cent (7.8 Gm. per 100 ml.); colour index, 1.1; M.C.V., 103.7 μ^3; M.C.H.C., 31.4 per cent; M.C.H., 32.5 $\mu\mu$g.; white blood cells, 6,200 per c.mm. Apart from pallor there were no signs of disease. Her appetite and diet had been excellent and she had been free from gastrointestinal disorder. The tongue was well papillated, and free HCl was present in the gastric juice. A Price-Jones curve showed a mean diameter of 7.72 μ, standard deviation 0.77 μ, coefficient of variation 9.9 per cent, megalocytosis 12 per cent, microcytosis nil. The marrow was megaloblastic. Plasma bilirubin was normal (0.24 mg. per 100 ml.) and methaemalbumin was not detected (175 mm. depth). In 24 hours the excretion of ketosteroids was 5.1 mg." Examination of two 24 hour specimens of urine, revealed the following results: pregnanediol, 30.3 and 28.5 mg.; total oestrogen (estimated as oestradiol), 11.8 and 12.5 mg.

"After a control period, 80 μg. of vitamin B_{12} was injected intramuscularly. There was no response and the marrow remained megaloblastic. A yeast extract also proved ineffective. Folic acid was then given daily, 2.5 mg. by intramuscular and oral routes alternately. Reticulocytes rose to a peak of 10.6 per cent on the fifth day, and in 10 days the red blood cells increased from 1,760,000 to 2,200,000 per c.mm. When the dosage was increased to 15 mg. daily reticulocytes rose again slightly to 3.2 per cent on the fifth day. After 10 days red blood cells numbered 2,860,000, but there was no further increase up to 20 days.

"When later she received 120 ml. of an aqueous liver extract daily the red blood cells increased to 3,630,000 in 10 days, but there was no further increase in 16 days, and haemoglobin fell from 63 per cent to 56 per cent (8.3 Gm. per 100 ml.), with M.C.V. 83.6 μ^3, M.C.H.C. 27.5 per cent, M.C.H. 23.7 $\mu\mu$g. On this account she was given ferrous sulphate, 1.2 Gm. daily. At the same time folic acid was restarted in doses of 20 mg. Two weeks later—six days before the child was born—the red blood cells numbered 3,650,000 per c.mm., with haemoglobin 67 per cent (9.9 Gm. per 100 ml.). After delivery, with no change in treatment, recovery was rapid, and in 12 days the red blood cells numbered 4,420,000, with haemoglobin 82 per cent (12.1 Gm. per 100 ml.). A Price-Jones curve at seven weeks gave normal values: mean diameter, 7.25 μ; standard deviation, 0.63 μ; coefficient of variation, 8.7 per cent; megalocytosis, nil; microcytosis, 0.8 per cent.

"Case 4.—Mrs. D., aged 25 was admitted to hospital with fever and anaemia two days after the delivery of her third child, which was healthy although 10 weeks premature.

"Two weeks before delivery she took to bed because of diarrhoea, vomiting, and loss of weight, but from the second month she had had increasing weakness, soreness and ulceration of the mouth and throat, with pain on swallowing. She was pale and thin. The tongue, though normally papillated, showed several small white ulcers. A urinary infection was quickly controlled with hexamine. Gastric analysis at first showed achlorhydria, but 10 days later free HCl was present. Red blood cells numbered 1,460,000 per c.mm.; haemoglobin, 31 per cent (4.6 Gm. per 100 ml.); M.C.V., 102.8 μ^3; M.C.H.C., 30.6 per cent; M.C.H., 31.1 $\mu\mu$g.; white blood cells, 15,100 per c.mm. The marrow was megaloblastic. Van den Bergh's test was negative and methaemalbumin was not detected (depth 160 mm.).

"After transfusion and a control period the red blood cells numbered 2,220,000, and 80 μg. of vitamin B_{12} was injected intramuscularly. Reticulocytes rose to 3.6 per cent on the sixth day, but after 15 days the red cell count and marrow picture remained unchanged. During subsequent treatment with yeast extract, folic acid, and marmite the red blood cells slowly

increased to 4,370,000 per c.mm. There was a reticulocytosis of 4.4 per cent on the fourth day of folic acid therapy.

"Case 5.—Mrs. E., aged 40, gave a doubtful history of anaemia following the birth of her fifth child, but had otherwise been healthy. In the third month of her sixth pregnancy she lost her appetite, ceased eating meat, eggs, and fish, and subsisted mainly on bread, milk, potatoes, fruit juice, and meat extract. In the fifth month she became listless and breathless, with swelling of the legs and, later, diarrhoea and headaches.

"When admitted at eight months she was obese, pale, dyspnoeic, and moderately oedematous. Blood pressure was 170/90 mm. Hg, blood urea 43 mg. per 100 ml. Marked albuminuria persisted until after parturition. The tongue was smooth. The red blood cells numbered 980,000 per c.mm.; haemoglobin, 20 per cent (3 Gm. per 100 ml.); M.C.V., 102 μ^3; M.C.H.C., 29.6 per cent; M.C.H., 30.2 $\mu\mu$g.; reticulocytes, 0.4 per cent; white blood cells, 3,000 per c.mm. Blood films showed macrocytosis and the marrow was megaloblastic. Gastric analysis later showed free HCl. Plasma bilirubin was 0.48 mg. per 100 ml. Methaemalbumin was not detected.

"The patient was transfused with cells from 560 ml. of blood, an equal volume of her own blood being removed simultaneously, using polythene catheters. At the same time 80 μg. of vitamin B_{12} was given intramuscularly. After 38 hours her condition remained serious, and as a response to vitamin B_{12} was unlikely she was given 30 mg. of folic acid intravenously. She was transfused then and again two days later because of epistaxis. Reticulocytes rose on the third day after folic acid, reaching a peak of 18.8 per cent on the seventh day, with clinical improvement. On the fifth day after folic acid she gave birth to a child, which died of cystic cerebral degeneration.

"Her condition improved without further treatment until the nineteenth day, when the red blood cells numbered 2,650,000 per c.mm., with haemoglobin 52 per cent (7.7 Gm. per 100 ml.). She was now given 20 mg. of folic acid daily by mouth, and after three weeks, two months, and four months the red blood cells numbered 4,310,000, 4,760,000, and 5,220,000 respectively. Treatment was stopped, and so far (two months) she has not relapsed.

"Case 6.—This patient, aged 26, was admitted four weeks after the birth of a full term normal child. Iron was prescribed early in pregnancy for pallor, which in the terminal three months became more pronounced and was accompanied by swelling of the feet. The dietary history was satisfactory. Labour was normal, with no serious blood loss, but afterwards she became much worse, having dyspnoea and palpitation even in bed. Iron therapy brought no relief.

"On admission she was extremely pale and slightly yellow. The tongue was smooth at the edges and clean, but never sore. The liver and spleen were just palpable. There was achlorhydria even after histamine and alcohol. Plasma bilirubin was 4.8 mg. per 100 ml. (direct reaction negative). Methaemalbumin was not detected. Thymol turbidity and thymol flocculation were normal. A fragility curve (after transfusion) showed a wide range from 100 per cent haemolysis at 0.34 to nil at 0.56 per cent saline, but the mean corpuscular fragility was just within normal limits. The red blood cells numbered 1,060,000 per c.mm.; haemoglobin, 24 per cent (3.6 Gm. per 100 ml.); reticulocytes, 4.6 per cent; colour index, 1.13; cell volume, 11 per cent; M.C.V., 103.8 μ^3; M.C.H., 33.5 $\mu\mu$g.; M.C.H.C., 32.3 per cent; white blood cells, 2,700. A Price-Jones curve showed mean corpuscular diameter 7.66 μ, standard deviation 0.98 μ, coefficient of variation 12.8 per cent, megalocytosis 12.8 per cent, microcytosis 1.0 per cent. The marrow was predominantly megaloblastic.

"The patient was transfused with erythrocytes, which could be separated by differential agglutination. Afterwards there was a spontaneous reticulocytosis of 38.6 per cent, with a transient rise of red blood cells. Nevertheless the blood from this and two other transfusions was rapidly destroyed and the total red cell count fell to 820,000 per c.mm. The injection of 80 μg. of vitamin B_{12} had no effect on the blood picture or on the haemolysis, and the marrow remained megaloblastic.

"The subsequent daily administration of 20 mg. of folic acid by mouth was followed by prolonged reticulocytosis, itself of doubtful significance because of the pre-

vious findings. After two weeks the rate of elimination of transfused red cells fell and subsequently became normal. The marrow was now normoblastic. The rise in the total red cell count flattened out at about 3,500,000, but normal levels were subsequently attained after prolonged treatment with refined liver extract ('examen' 10 ml. every 2 weeks for 10 weeks, supplemented latterly with iron). For the past three months the patient has remained well without treatment. The blood picture is normal and the liver and spleen are not palpable."

"The injection of vitamin B_{12} in doses of 65 to 80 μg. was ineffective in 6 patients with megaloblastic anaemia associated with pregnancy or the puerperium, all of whom subsequently responded to folic acid, usually 2.5 mg. daily."

Vitamin B_{12} in Macrocytic Anaemia of Pregnancy and the Puerperium — PATEL, J. C. AND KOCHER, B. R. — *British Medical Journal*, 1: 924 (April 22) 1950.

"The effect of vitamin B_{12} is described in 5 cases of macrocytic anaemia of pregnancy and the puerperium."

"In all cases except one 40 μg. was given in a single intramuscular injection. The period of observation was 14 days, and improvement was judged by the formula of Dyke and Della Vida, in which $I = 0.93\text{-}0.214Eo$, where I is the weekly increase in millions of red blood cells and Eo is the original level of red blood cells.

"Case 1.—A woman aged 30 was admitted in the eighth month of her fourth pregnancy complaining of increasing general weakness for the past two years, which had become marked during the past three months. She had pronounced nausea and vomiting during the earlier months of pregnancy; and this had prevented her from taking adequate nourishment. Slight nausea persisted throughout the pregnancy. She gave a history of diarrhoea off and on during the previous three months. One month before admission she had had irregular fever with chills for 21 days. She also complained of stomatitis and had had oedema of the feet for a month. There had been no difficulties in previous pregnancies and her family history was without significance. She used to eat a mixed diet before her illness, but owing to her nausea and diarrhoea she now ate mostly rice and dal."

"On examination she had puffiness of the face and oedema of the legs, and was very severely anaemic. Her tongue was smooth and red at the tip. Examination of her heart disclosed a haemic murmur. Other systems were normal. Her blood count was: red cells 880,000 per c.mm.; haemoglobin 3.5 Gm. per cent; leukocytes, 4,400 per c.mm.; M.C.V., 125 μ^3; M.C.H.C., 31.8 per cent; platelets, 80,000 per c.mm.; icterus index, 5; van den Bergh test, negative. Total proteins were 5.14 Gm. per 100 ml. The bone marrow was megaloblastic. The gastric contents contained free hydrochloric acid. The Wassermann reaction was negative. Analysis of urine revealed nothing abnormal. Stool examination showed the presence of ova of roundworm and cysts of *Endamoeba histolytica*. A blood count two days later showed: red cells, 720,000 per c.mm.; haemoglobin, 3.5 Gm. per cent; M.C.V., 145.8 μ^3; M.C.H.C., 33.3 per cent; leukocytes, 3,900 per c.mm.

"At this stage the patient was given 40 μg. of vitamin B_{12} in one single injection. The reticulocyte peak occurred on the fifth day (highest 28.9 per cent). She felt hungry on the third day and by the fifth day she was very hungry. Most of her symptoms improved, including the glossitis. The count at the end of 10 days was: red cells, 1,690,000 per c.mm.; haemoglobin, 5.5 Gm. per cent; M.C.V., 109.3 μ^3; M.C.H.C., 29.9 per cent; leukocytes, 9,750 per c.mm. The blood count at the end of 14 days was: red cells 1,500,000 per c.mm.; haemoglobin, 5 Gm. per cent; M.C.V., 120 μ^3; M.C.H.C., 27.7 per cent; leukocytes, 9,700 per c.mm. On the sixth day the bone marrow still showed a few megaloblasts. On the eighteenth day the red blood cells numbered 1,530,000, and the haemoglobin was 4.75 Gm. per cent; she was at this stage treated with crude liver extract, as the supply of vitamin B_{12} was insufficient. She left the hospital against medical advice."

"The response to 40 μg. of vitamin B_{12} was suboptimum and was maximum about the tenth day; the blood level declined by the eighteenth day. This suggests that 40 μg. was the suboptimum dose. It is also

corroborated by the failure of that amount of vitamin B_{12} to convert the bone marrow to a completely normoblastic picture.

"Case 2.—A woman aged 25 was admitted in the sixth month of her second pregnancy for general weakness and giddiness of 12 months' duration. She had left Pakistan 14 months before owing to the partition of the country, and her first child had been delivered within two months of her arrival in India. Since then she had been ailing. She had had an attack of malaria lasting for a period of two months, for which she had been treated in a refugee camp. She had had stomatitis off and on, and diarrhoea, four to five stools a day, for a period of five months. She also complained of pain in the chest, with a blood-stained sputum, two months previously. Her appetite had been poor for the past five months.

"On examination she was pale and emaciated, her tongue was pale and smooth, and her spleen was palpable 4 finger-breadths below the costal margin. Other systems were normal. A blood count showed: red cells, 870,000 per c.mm.; haemoglobin, 4 Gm. per cent; M.C.V., 160.9 μ^3; M.C.H.C., 28.5 per cent; leukocytes, 3,500 per c.mm. The van den Bergh reaction was negative, and the icterus index was 5. The bone marrow showed a megaloblastic picture. Platelets numbered 85,200 per c.mm., the Wassermann reaction of the blood was negative, and total proteins were 6.72 Gm. per 100 ml. Analysis of the urine showed nothing abnormal. Stool examination revealed a few ova of *Ancylostoma duodenale*, and the gastric contents contained free acid.

"The patient came from a very poor family. Her diet was mixed, but owing to stomatitis and diarrhoea she could not eat more than small quantities of rice and dal. Her blood count two days after admission was: red cells, 840,000 per c.mm.; haemoglobin, 3.5 Gm. per cent; M.C.V., 190.4 μ^3; M.C.H.C., 21.8 per cent; leukocytes, 2,700. She was given 40 μg. of vitamin B_{12}. She felt hungry on the third day and her diarrhoea subsided within a week. The highest reticulocyte count was 17.4 per cent on the sixth day. At the end of 14 days her blood count was: red cells, 2,350,000 per c.mm.; haemoglobin, 8.25 Gm. per cent; M.C.V., 123.3 μ^3; M.C.H.C., 27 per cent; leukocytes, 2,650 per c.mm. The day after the reticulocyte crisis the bone marrow still contained a few megaloblasts. On the nineteenth day after the institution of treatment her blood count was still improving: red cells, 2,770,000 per c.mm.; haemoglobin, 9 Gm. per cent; M.C.V., 120.9 μ^3; M.C.H.C., 26.8 per cent; leukocytes, 3,600. She left the hospital at this stage, as she had improved and was anxious to look after her first child."

"Case 3.—A woman aged 22 was admitted to hospital in the eighth month of her fourth pregnancy. She had had general weakness for three months, low fever for 15 days, oedema of feet for five days, and constipation and dry cough for a week. She had a similar history during her previous pregnancies."

"On examination she was pale, with puffiness of the face and oedema of the feet. Her tongue was smooth and pale. Other systems did not reveal any abnormality. Her blood count was: red cells, 1,000,000 per c.mm.; haemoglobin, 2 Gm. per cent; M.C.V., 110 μ^3; M.C.H.C., 18.1 per cent, leukocytes, 4,800 per c.mm. The van den Bergh reaction was negative, and the icterus index was 3. Platelets numbered 72,000 per c.mm. The Wassermann reaction of the blood was negative. The bone marrow showed megaloblastic reaction. Gastric analysis revealed the presence of free acid. A few pus cells were seen on microscopical examination of the urine. Stool examination revealed a few cysts of *Giardia lamblia*. Serum proteins were 5.47 Gm. per cent. Two days later her blood count was: red cells, 980,000 per c.mm.; haemoglobin, 2 Gm. per cent; M.C.V., 122.8 μ^3; M.C.H.C., 16.6 per cent; leukocytes, 4,200 per c.mm. She was given 40 μg. of vitamin B_{12}. The highest reticulocyte count was 24 per cent on the fifth day. Her blood count at the end of 14 days was: red cells, 2,910,000 per c.mm.; haemoglobin, 7.25 Gm.; M.C.V., 94.4 μ^3; M.C.H.C., 26.3 per cent; leukocytes, 8,600 per c.mm. Her blood count increased during the next few days, when she had labour pains and delivered prematurely. Her bone marrow picture on the day after the highest reticulocyte count had turned completely normoblastic."

"Case 4.—A 16 year old primipara was admitted to hospital in the sixth month of pregnancy. She complained of general weakness for three months, dyspnoea on exertion for eight days, cough with expectoration for 1½ months, sore tongue for 15 days, backache, and pain in the abdomen. The usual morning sickness in the early period of pregnancy had occurred. She had had attacks of fever, probably malaria, two years previously.

"On examination she was pale, with puffiness of the face, and her tongue was smooth and red at the tip and margins. Her spleen was palpable 2 fingerbreadths below the costal margin; the liver was not palpable. There was a haemic murmur. Other systems were normal. She did not give any history of abortions. On admission her blood count was: red cells, 630,000 per c.mm.; haemoglobin, 2.5 Gm. per cent; M.C.V., 126.9 μ^3; M.C.H.C., 31.2 per cent; leukocytes, 8,300 per c.mm. (polymorphonuclear leukocytes 60 per cent, lymphocytes 38 per cent, eosinophils, 2 per cent, monocytes nil). The van den Bergh reaction was negative, and the icterus index was 5. The Kahn reaction was negative. Serum proteins were 5.14 Gm. per cent. Examination of the stool and urine revealed nothing abnormal. Gastric analysis disclosed the presence of free acid. Marrow from the sternum showed megaloblastic reaction. The patient was transfused with 250 ml. of blood. The blood count after transfusion was: red cells, 1,040,000 per c.mm.; haemoglobin, 3.25 Gm. per cent; M.C.V., 100 μ^3; leukocytes, 5,400. It remained at that level for five days. On the eleventh day after transfusion the blood level was: red cells, 920,000 per c.mm.; haemoglobin, 3.5 Gm. per cent; M.C.V., 118.4 μ^3; M.C.H.C., 33.3 per cent; leukocytes, 6,700 per c.mm. At this stage she was given 40 μg. of vitamin B_{12}. The highest reticulocyte response was 27.3 per cent on the fifth day after the first injection. On the seventh day the bone marrow had turned normoblastic except for a few megaloblastic cells. Her appetite increased by the fourth day and she felt better. Her stomatitis improved by about the eighth day. The blood count on the fourteenth day was: red cells, 2,350,000 per c.mm.; haemoglobin, 6.75 Gm. per cent; M.C.V., 93.6 μ^3; M.C.H.C., 30.6 per cent.

"The blood count on the seventeenth and twentieth days was about the same, so on the latter day she was given a second injection of 40 μg. of vitamin B_{12}. A reticulocyte peak was 12.8 per cent on the fifth day after the second injection. The blood count at the end of the tenth day after the second injection was: red cells, 3,020,000 per c.mm.; haemoglobin, 8 Gm. per cent; M.C.V., 86 μ^3; M.C.H.C., 32.5 per cent. The blood count on the twelfth and fourteenth days was slightly less than the above, and so a third injection of vitamin B_{12} (40 μg.) was administered on the latter of these days. The reticulocyte peak was 5 per cent on the fifth day. The blood count on the tenth day after the third injection was: red cells, 3,720,000 per c.mm.; haemoglobin, 10 Gm. per cent; M.C.V., 86.2 μ^3; M.C.H.C., 31.2 per cent. On the fourteenth day after the third injection it was: red cells, 3,210,000 per c.mm.; haemoglobin, 9.5 Gm. per cent; M.C.V., 96.5 μ^3; M.C.H.C., 29.6 per cent. At this stage the patient was given 20 μg. of vitamin B_{12}, but she could not be persuaded to stay in the hospital any longer. She kept well and was delivered uneventfully at full term, at a place outside Bombay."

"This case of pregnancy anaemia was followed during the patient's 55 days' stay in hospital. Vitamin B_{12}, in 40 μg. dosage, was effective, and produced optimum response, but the effect did not last beyond the tenth day after each injection in all the three periods of 14 days. The blood level reached its highest by the tenth day and remained stationary or had diminished by the fourteenth day. This suggests that in this particular case 40 μg. of vitamin B_{12} is just enough to produce the optimum effect, or perhaps slightly less than the amount needed.

"Case 5.—A woman aged 25 was admitted to hospital for increasing general weakness for the past six months, which had worsened since the delivery of an 8 month child six weeks before. Her weakness increased to such an extent that she had been bedridden during the last 15 days. She also complained of dyspnoea on exertion, palpitation, giddiness, anorexia, stomatitis, low fever, occasional attacks

of diarrhoea and vomiting, and loss of weight. All these symptoms were present during her pregnancy, but she gradually became worse during the last six weeks. She was a Para III, and her previous two deliveries were normal. There was no relevant history of previous illness.

"On examination she was very pale, the tongue was pale and smooth, the liver and spleen were not palpable, and a haemic murmur was heard at the cardiac area. Other systems were normal. A blood count showed: red cells, 680,000 per c.mm.; haemoglobin, 3 Gm. per cent; leukocytes, 8,200 per c.mm. She was given a blood transfusion of 250 ml. The blood level after transfusion increased as follows: red cells, 1,240,000 per c.mm.; haemoglobin, 4.5 Gm. per cent; M.C.V., 112.9 μ^3; M.C.H.C., 32.1 per cent; leukocytes, 8,750 per c.mm. Five days after blood transfusion the blood level declined: red cells, 680,000 per c.mm.; haemoglobin, 3 Gm. per cent; M.C.V., 132.3 μ^3; M.C.H.C., 33.3 per cent. Other findings were icterus index, 6; indirect van den Bergh reaction, negative; differential leukocytic count, polymorphonuclear leukocytes 60 per cent, lymphocytes, 39 per cent, eosinophils 1 per cent, monocytes nil. There were 12 per cent normoblasts in the peripheral blood smear. The Kahn reaction was negative; serum protein 5 Gm. per cent. Urine and stool examination revealed nothing abnormal. The gastric contents contained free acid, and the bone marrow was megaloblastic.

"She was given 20 μg. of vitamin B_{12}. The highest reticulocyte peak was 17 per cent on the sixth day after the starting of treatment. The blood count increased on the seventh day: red cells, 1,040,000 per c.mm.; haemoglobin, 3.75 Gm. per cent; M.C.V., 120 μ^3; M.C.H.C., 31.2 per cent. On the tenth day it decreased: red cells, 960,000 per c.mm.; haemoglobin, 3.5 Gm. per cent; M.C.V., 125 μ^3; M.C.H.C., 29.1 per cent; leukocytes, 6,500 per c.mm. She felt better and her appetite had improved on the fourth day, but from the eighth day onwards her general condition deteriorated. At this stage she was given 20 μg. of vitamin B_{12} on two consecutive days. The reticulocyte peak (20.8 per cent) occurred on the eighth day after the second injection. Her general condition improved considerably. She regained her appetite and her looseness of bowel had improved. Her blood level on the tenth day after the second injection was: red cells, 1,850,000 per c.mm.; haemoglobin, 6.5 Gm. per cent; M.C.V., 121.6 μ^3; M.C.H.C., 28.9 per cent. On the fourteenth day it was: red cells, 2,030,000 per c.mm.; haemoglobin, 6.5 Gm. per cent; M.C.V., 108.3 μ^3; M.C.H.C., 29.5 per cent. On the seventeenth day the blood level declined: red cells, 1,930,000 per c.mm.; haemoglobin, 6 Gm. per cent; M.C.V., 106.1 μ^3; M.C.H.C., 29.2 per cent. She was further treated with crude liver extract owing to the scarcity of vitamin B_{12}."

"Anaemia in this case was present during the later part of pregnancy, and remission did not occur after the termination of pregnancy as it sometimes does. On the contrary, the condition deteriorated. On this account the case is considered as one of pregnancy anaemia treated during the puerperium. Injection of 20 μg. of vitamin B_{12} produced partial improvement, both clinical and haematological, but this had declined by the tenth day. While 40 μg. produced a haematological response which was maximum by the tenth day and was sustained till the fourteenth day, it was suboptimum judged both by reticulocyte response and by the red blood cells and haemoglobin. This case also illustrates that more than 40 μg. of vitamin B_{12} is needed to produce optimum haematological improvement even during a period of 10 days."

The Ocular Signs of Intracranial Hypertension—Voisin, J.—*La presse médicale*, 58: 421 (April 19) 1950.

Examination of the eyegrounds is indispensable in intracranial hypertension and aims at determination of one of the major although inconstant signs of this hypertension; namely, papillary stasis, and of ocular signs of cerebral localization, including alterations of the visual field, oculomotor or pupillary disturbances, optic atrophy and others.

The main ocular sign of intracranial hypertension is objective, consisting in a bilateral edema of the papillae. In some cases this papillary edema is preceded by a stage of papillary hyperemia which is always difficult to evaluate. Determination

of the pressure in the central retinal artery should furnish important information, as one writer's work indicated that a phase of hypertension in this artery precedes the phase of papillary edema in two thirds of the cases, but another frequently demonstrated hypotension in this artery in intracranial tumors of the anterior and middle fossa.

In its beginning, papillary edema may be difficult to determine particularly if it is localized at the papillary border or the points of emergence of the vascular trunks. The diagnosis will be afforded in such cases on the basis of blurring of the contour, disappearance of the rings delimiting the papilla and the cloudy blurred aspect of the vessels where they pass this point. At this stage papillary edema raises delicate diagnostic problems, particularly if it does not appear at the same time on both sides. The blurring of the papillary borders may be due to infiltration of a hematic nature, retinal exudations, or disturbances of the posterior layers of the vitreous body, and associated frequently with a slight bulging, it may be of congenital origin or may be caused by ametropia; namely, myopia, astigmatism and particularly hypermetropia in which the papilla assumes the aspect of pseudoneuritis. Papillary edema may be caused by inflammation of the optic nerve (beginning papillitis) or the adjacent choroid rather than by intracranial hypertension, without always giving rise to Jensen's juxtapapillary chorioretinitis, and it also may denote the beginning of neuroretinitis of Bright's type. There is also a possibility of congenital alterations of the borders of the papilla like colobomas, myelin fibers and hyaline verrucosities, and of acquired alterations like a senile or glaucomatous halo. Finally, unilateral papilledema may be caused by orbital factors (tumors) or ocular factors (traumatic or surgical hypotension) and may develop into unilateral stasis.

Thus doubt concerning the diagnosis of papillary edema from intracranial hypertension may persist after the first examination; repetition of the examination at intervals of a week will permit differentiation between a congenital modification which will remain unchanged and edema which will increase or decrease. One writer tried to establish a definite distinction between papillary stasis with a bulging of more than 2 diopters, and optic neuritis with a bulging of less than 2 diopters, but this has only led to confusion. The term of neuritis should be reserved exclusively for inflammatory affections of the optic nerves which in the case of papillitis will be associated with edema of the papilla. The term of papillary stasis may be applied to any papillary edema regardless of its intensity, as it does not reveal a primary affection of the optic nerve but constitutes the manifestation of a lesion which is often remote and intracranial and which modifies the normal circulation of the nerve, but it seems more logical to speak of papillary stasis only in cases in which the blurring of the border is associated with an impression of bulging and with definite modifications of the veins which will appear kinked, tortuous and turgescent.

At the peak of the condition edema and vascular modifications become maximal. The bulging of the papilla may form a true fungous formation and is constituted by edema of a frequently translucent aspect. Its degree can be evaluated readily by means of the ophthalmoscope with an upright picture and in extreme cases the bulge may reach 2 mm. or exceed this amount. The papillary border will be effaced and often striated radially, and the edema will extend to the surrounding retina, particularly along the vessels, resulting in an enlargement of the papilla. The vessels will run in curves after their central emergence and will be kinked or appear interrupted at the papillary border. The veins will be tortuous and markedly dilated while the arteries are frequently normal or narrowed. The papilla will assume a more intense red coloration than normally and will contrast less with the color of the adjacent retina; this redness is sometimes caused by fine superficial hemorrhages, and additional retinal hemorrhages may be distributed radially at the border of or along the vessels. The peripapillary retina may show small white exudations distributed in narrow striae at the borders or in the form of points or plaques in the papillomacular region. At this stage the subjective visual disturbances may make their appearance, having been preceded by headache, nausea and vomiting. There will be periods of a few sec-

onds during which vision becomes cloudy or even completely abolished, turning to normal again immediately afterwards, and these periods may occur at short intervals. Diplopia due to involvement of the external oculomotor nerve is frequent in the syndrome of intracranial hypertension, as this long delicate nerve reacts readily, and convergent strabismus with homonymous diplopia loses the value of localization which it would have had if the paralysis had been an early sign. The visual acuity remains normal for a long time and the functional disturbances are minimal; namely, enlargement of Mariotte's plaque and slight reduction of the visual field. More intense alterations of the visual field announce the appearance of the atrophic phase (nasal narrowing and Bjerrum's type of scotoma sometimes with nasal course) or are independent of the stasis and reveal the localization of the causative tumor.

This dissociation between the intensity of the ophthalmoscopic signs and the insignificance of the functional disturbances is of the highest value in the differential diagnosis. The papillary bulging caused by papillitis always remains moderate, and the neuritic involvement usually remains unilateral while the papillary stasis from intracranial hypertension is usually bilateral. Although bilateral papillary edema forms part of the syndrome of neuroretinitis of arterial hypertension differentiation from intracranial hypertension is easy in typical cases. The papillary edema is less marked in neuroretinitis and is associated with arterial modifications, hemorrhages and retinal exudations which extend to the entire posterior pole of the eyeball and which rapidly impair vision. However, in progressing, papillary stasis may lead to retinal hemorrhages away from the papilla and even to exudations which may be located in the macula and which may also produce a macular star. Furthermore, malignant arterial hypertension may produce typical papillary stasis due to cerebromeningeal edema and this pseudotumoral form of arterial hypertension poses an etiologic rather than a differential diagnostic problem. For diagnostic orientation one should concentrate on the general arterial, cardiac and renal signs and their course under the influence of treatment rather than on the condition of the retinal arteries and pressure. The problem may become delicate when a tumor of the posterior fossa causes arterial hypertension and azotemia or when a tumor develops in a hypertensive patient, and then ventriculography or simple ventricular puncture may solve the problem, revealing the ventricle in place and usually not dilated in cerebral edema.

Bilateral papillary stasis usually indicates intracranial hypertension, but in exceptional cases it is associated with ventricular hypotension; only ventricular puncture can determine the tension of the cerebrospinal fluid and will be the most reliable guide for the neurosurgeon in comatose conditions. Rather frequently the papillary bulging is more marked on one side but this finding does not permit any definite conclusion as to the localization of a tumor or neoformation. However, in Kennedy's syndrome of unilateral papillary stasis with optic atrophy with sharp borders on the other side, tumor localization is based on the sign of direct compression of the optic nerve causing atrophy if a tumor of the hemispheres is suspected, although this syndrome loses its localizing value in tumors associated with hydrocephalus.

It becomes more rare to have to make a diagnosis of papillary stasis at a late stage when diminution of the visual acuity, often associated with particularly nasal narrowing of the visual field, indicates development towards optic atrophy and blindness which then often cannot be arrested any longer by a surgical intervention. At this stage the papilla will turn pale and will flatten slightly; it will become dull white, sometimes with plaques of hemorrhagic residue, its diameter will remain enlarged, its borders will remain irregular, sometimes marked by fine black pigments, and the veins will preserve their turgescence and tortuosity for a long time. Interpretation may be difficult at this stage, as papillary stasis of long standing, having reached the stage of atrophy, or secondary edema diminishing the definiteness of a primary optic atrophy may be dealt with.

The visual prognosis of papillary stasis is grave in itself; its study will differ in cases in which it represents a capital diagnostic sign and in cases in which it in-

dicates a complication in the course of an established affection. There is the stasis of tumors and nontumorous cerebral neoformations and of pseudotumoral syndromes of encephalitis and of certain malacias of arterial hypertension on the one hand, and that of trauma and meningitis on the other hand. Special clinical aspects deserving mention, include acute papillary stasis with pupillary sluggishness in the adult, the pseudodigestive form of the syndrome of blocked hydrocephalus in the child, and hemorrhagic pachymeningitis justifying subdural puncture in the infant.

In practice the finding of papillary stasis should orient the diagnosis towards the possibility of an intracranial neoformation, except under special circumstances, and should form an absolute contraindication to spinal puncture. The indications for surgical intervention will depend on the ophthalmologic findings. However, not all tumors cause papillary stasis and some do not cause it until at a late stage of development, and therefore, if doubt persists a normal aspect of the eyegrounds should not keep one from instituting complementary studies, among which ventricular puncture and ventriculography are the most important ones.

Mitral Stenosis. Its Surgical Treatment by Commissurotomy — GLOVER, ROBERT P., O'NEILL, THOMAS J. E. AND BAILEY, CHARLES P.—*Pennsylvania Medical Journal*, 53: 375 (April) 1950.

A method is presented for the relief of mitral stenosis whereby the production of regurgitation has been so minimized as to be not significantly greater than that which inherently exists with all mitral stenosis, by its very nature.

"Careful clinical examination and appraisal by an experienced cardiologist is obviously essential. His armamentarium has long included, in addition to subjective and auscultatory analysis: (1) electrocardiograms and sound recordings; (2) teleoroentgenograms, esophagograms, and fluoroscopy for an estimation of the size of individual heart chambers; (3) exercise tolerance tests; and (4) laboratory data for the detection of rheumatic activity . . . . (5) estimations of cardiac output at rest and with exercise as calculated by ballistocardiography or, more accurately, by utilization of the Fick principle; and (6) determinations of the pulmonary arterial and right ventricular pressures by cardiac catheterization."

"The possible surgical approaches to the problem of mitral stenosis seem to take one of the following three courses:

"1. Methods of by-passing the stenotic mitral valve.

"2. Methods of relieving the associated pulmonary hypertension.

"3. Methods of direct surgical attack upon the stenotic valve."

"It is sufficient to state that methods of by-passing the stenotic valve have as yet been carried out only on an experimental basis and are not sufficiently developed to warrant clinical trial. Methods of relieving the associated pulmonary hypertension by producing a shunt between the pulmonary and systemic venous systems, although of some merit, seem to be of such a palliative nature only that no long-lasting benefit can reasonably be derived by the patient and are, therefore, undesirable provided direct and successful attack upon the damaged mitral valve can be accomplished."

As to the third method of surgical approach, there have been a number of direct attacks upon the stenotic mitral valve. It is the writers' considered opinion that the approach through the auricular appendage is far superior to any other. "It leads directly into the wide opening of the mitral funnel and thence to its stenotic orifice. There are no chordae tendineae to interfere with the passage of the instruments or finger. In addition, no serious disturbance of cardiac rhythm or function is produced. The finger or instrument is well tolerated in the roomy left auricle, unless the actual passage of blood into the ventricle is obstructed for more than three beats. In addition, the appendage may be readily and securely ligated at completion of the operation.

"On the other hand, the left ventricular approach is obstructed by chordae tendineae and does not insure ready or accurate localization of the small opening of the mitral funnel. Such an approach may provoke a serious arrhythmia, does not permit digital insertion or palpation, and may be difficult to close securely."

Commissurotomy is a term suggested to designate the procedure which the writers have employed to reestablish a marked degree of normal mitral valve function. Their present operative technique is simplified and direct. "With the patient in the supine position, the left arm over the head, an incision is made over the left third rib or in the inframammary fold. The third rib is removed, including the costal cartilage. The cartilages of ribs two and four may be divided. The pleura is opened through the incised rib bed. The lung is permitted to collapse. The pericardium is incised longitudinally, one-half inch anterior to the phrenic nerve, for 3 inches. Care must be taken not to extend the incision too far toward the apex, lest the heart have a tendency to herniate from its sac. The huge distended auricular appendage now protrudes. The pericardial sac is sprayed with 5 per cent procaine and additional procaine is injected under the epicardium encircling the base of the auricular appendage. A purse-string suture of heavy braided silk on an atraumatic needle is passed about the appendage through this injected area. A Satinsky clamp is now closed over the base of the appendage and a generous portion of its tip is amputated. This piece serves for heart muscle biopsy.

"All intra-appendageal trabeculae that might interfere with insertion of the finger are divided. Two gloves are worn on the right hand. An opening is made in the outer one on the palmar surface at the base of the index finger, and another at the tip. The blade of the commissurotomy knife is inserted between the gloves on the index finger, and the finger is inserted into the left auricle as the clamp is released. The finger is well tolerated by the auricle and causes no disturbance unless the mitral opening is actually obstructed by the finger tip for several beats. The valve is easily located, and is explored. Its structure is estimated and the size of the opening and the location of the commissures are determined. The knife is now protruded through the orifice and the hook is engaged upon the anterolateral commissure. A backward stroke divides the commissure, usually adequately the first time. The finger again palpates the opening and gently dilates it.

"Sometimes there are remaining fibrous strands which require either digital separation or actual division with the knife. If the cut in the commissure does not extend well into normal tissue, it is repeated." In cases which have a rather soft valve orifice markedly diminished in cross sectional area, simple opening of the lateral commissure is in the writers' opinion sufficient. "On the other hand, with a rigid, fixed, and sometimes calcified valve, incision of only one commissure would undoubtedly be inadequate." In such more advanced cases the writers reinsert the knife through the orifice by simple pronation of the hand, bringing the blade into apposition with the posteromedial commissure, which is then divided.

"Having inserted the finger once more through the enlarged opening to make sure of its mobility and function, the finger and knife are deftly withdrawn from the auricle. The previously placed purse-string suture is drawn tight, preventing more than a few cubic centimeters of blood loss. The suture is tied, and the cut edge of the appendage is oversewn. There should be no disturbance of the systemic circulation and few irregularities throughout the procedure. The pericardium is left open and the pleura is drained. The chest wall is closed in layers.

"Postoperatively, the patient may experience considerable pain for three to four days from the 'chemical' pericarditis produced by manipulation. This is controlled by opiates. Ambulation is permitted within two to five days."

It is the writers' present belief that commissurotomy by such a technique is a simple, relatively safe, direct method of reestablishing improved valve function. "It has the great advantage of direct digital guidance." It should not, and has not in any of the 5 successful cases, produced any detectable amount of mitral regurgitation. "Blood loss is minimal and no apparent disturbance to heart function results. That it effectively accomplished the desired result is shown not only by the marked clinical improvement in all living patients but also by objective physiologic studies."

"In none of these cases was there any appreciable blood loss, significant change

of rate or rhythm, or disturbance of systemic circulation."

"Commissurotomy by the technique described was performed in 8 cases with 3 fatalities." In the first of these a modified scalpel was employed, as the present commissurotomy knife had not been perfected. "Attempts to incise the commissure were attended by repeated disengagement of the blade as it rode over the fibrotic valve, resulting in an inadequate incision extending only a few millimeters into the scar tissue. Preoperative and postoperative pressure determinations in the left auricle were unchanged (320 mm. water). The patient died on the sixth postoperative day in pulmonary edema from unrelieved mitral stenosis. The second patient was operated upon accurately and well, and appeared to be on the way to a most satisfactory result, but suffered a cerebral embolus and died suddenly on the seventh postoperative day. Autopsy disclosed an adequate and satisfactory commissurotomy. Thrombus formation had occurred in the left auricular appendage, from which the embolus apparently originated." The writers had simply oversewn the incision in the appendage at the conclusion of the procedure. In 6 succeeding cases they ligated the auricular appendage at its base to prevent such disaster. "The appendage of the third patient operated upon shortly thereafter was ligated at its base without suture of the cut tip. Autopsy indicated that hemorrhage had occurred from this site. This experience led to both ligation at the base and an oversewing suture at the cut tip in all subsequent cases.

"The remaining 5 cases represent most satisfactory results. Four patients are clinically well. Two who had been digitalized for some months prior to surgery no longer require such medication." There was definite diminution in the size of the heart. "Their tolerance for exercise is remarkably increased, permitting them to return to normal activity. Careful examination reveals some slight residual evidence of mitral stenosis in 2 of the patients and somewhat more in a third in whom conditions were not satisfactory for an ideal commissurotomy. The others seem to have no residual signs of the disease, although they are admittedly short term follow-ups. Electrocardiographic follow-up shows no significant change from the preoperative state. There has been no evidence of increased mitral regurgitation in any of the 5."

"The indications and contraindications for commissurotomy must be considered together. Both must change as experience dictates." Common sense and present experience have led to certain conclusions to date:

1. Most favorable group.
   - A. Excessive fatigability.
     Increasing exertional dyspnea.
   - B. No rheumatic activity.
     Normal sinus rhythm.
     Lesion predominantly stenosis.
     Evidence of significantly increasing pulmonary hypertension.
2. Less favorable group.
   The above plus:
   - A. Recurrent bouts of hemoptysis.
   - B. Arterial embolic phenomena.
   - C. Auricular fibrillation without failure.

It follows then that the contraindications would be:

"1. Active rheumatic infection.
"2. Presence of superimposed subacute bacterial endocarditis.
"3. Cardiac failure uncontrollable by medical means.
"4. Presence of marked associated mitral regurgitation or other valve (aortic) deformities."

Aureomycin in Brucellosis — LINDECK, E. W. — *British Medical Journal*, 1: 985 (April 29) 1950.

Four cases of *Brucella abortus* infection treated by aureomycin are reported.

"Case 1.—A man aged 61 gave one month's history of a febrile illness before his admission to hospital. The agglutination for *Br. abortus* was found to be positive up to a titre of 1/2,500. On the fifth day after admission he was given aureomycin, 0.25 Gm. twice a day, and as no reaction to this dosage had occurred 0.25 Gm. was given three hourly and continued for nine days (total amount, 18.5 Gm.). His temperature became normal in 72 hours. During the course of treatment he experienced some indigestion. There has been no relapse since discharge from hospital 23 weeks ago.

"Case 2.—A youth aged 14 gave six weeks' history of frontal headaches; there had been no response to a course of a sulphonamide drug. His blood was found to agglutinate *Br. abortus* up to a titre of 1/5,000. The white cells numbered 6,200 per c.mm. (polymorphs 30 per cent, lymphocytes 51 per cent, monocytes 11 per cent, eosinophils 7 per cent, basophils 1 per cent). On the sixth day after admission he was treated with 16 Gm. of aureomycin spread over 12 days; 0.25 Gm. being administered twice a day on the first two days, and then four hourly. The temperature subsided permanently in 72 hours. When seen eight weeks later his spleen was still palpable, which suggests the possibility of some residual infection; his agglutination titre still remained 1/5,000. Twenty-three weeks later there had been no relapse.

"Case 3.—A man aged 46 gave a history of a P.U.O. lasting several months; his blood was found to be positive to *Br. abortus* up to a dilution of 1/2,500. Leukocytes numbered 7,600 (polymorphs 32 per cent, lymphocytes 63 per cent, monocytes 5 per cent). A full course of sulphadiazine produced no improvement. Aureomycin was then begun, 0.1 Gm. being administered in five divided doses on the first day; this was followed by divided doses of 0.6 Gm. on the second day, 1.5 Gm. on the third day, and then 2 Gm. for three more days—a total of 8.2 Gm. On the second day of treatment his temperature rose to a higher level than before, but on the fourth day it became normal, and remained so until a relapse took place four months later. On this occasion, the agglutination titre was 1/500. Leukocytes numbered 5,500 (polymorphs 61 per cent, lymphocytes 33 per cent, monocytes 6 per cent). Aureomycin, 6.2 Gm. was given on the same plan as before, the temperature subsiding in 48 hours. The patient has remained well for eight and a half months.

"Case 4.—A woman aged 25 came with a three month history of ill health with intermittent pyrexia. She showed a rising titre of agglutination to *Br. abortus* of 1/250 to 1/500. Aureomycin, 0.75 Gm., was administered four hourly for 10½ days (total quantity, 47.25 Gm.). She experienced nausea and one vomiting attack during treatment. The temperature subsided on the fourth day and there has been no relapse in six months."

"Brucellosis is notoriously a relapsing disease, which makes any claim of cure difficult to substantiate dogmatically after such comparatively short follow-up periods, but in every case quoted aureomycin has at least interrupted the rhythm of the febrile paroxysms, and the patients have been symptom free."

There is no standardized dosage.

In the present state of knowledge it would therefore appear reasonable, in an average case of brucellosis to employ aureomycin in doses of 4 to 6 Gm. daily for a fortnight, with smaller amounts on the first three days (0.1 Gm., 0.6 Gm., and 1.6 Gm. in divided doses). "The ease of administration by the oral route and the lack of important side effects are important considerations." Should the case prove resistant or relapse frequently, a combination of aureomycin (3 Gm. in divided doses daily) and dehydrostreptomycin (1 Gm. twice a day intramuscularly for 12 to 14 days) might well be employed.

Pediatrics

Simultaneous Immunization of Young Children Against Diphtheria, Tetanus, and Pertussis. Experience in a Northern Metropolitan Area — SAUER, LOUIS W. AND TUCKER, WINSTON H. — *American Journal of Public Health*, 40: 681 (June) 1950.

"This report deals with the results of administration of an alum-precipitated mixture of diphtheria and tetanus toxoids with pertussis vaccine to two groups of infants. Group I consisted of infants 6 or more months of age who received three monthly doses of 0.5 ml. of the antigenic mixture. Group II were infants who received four monthly doses of 0.5 ml. at 3, 4, 5, and 6 months of age. Tests for immunity were performed three months after the final dose of multiple antigens."

"The alum-precipitated mixture of diphtheria and tetanus toxoids with pertussis vaccine used in groups I and II was a combination of refined diphtheria and tetanus toxoids and phase I pertussis vaccine. It was standardized to contain in each milligram of antigen twice the necessary amounts of diphtheria and tetanus toxoids and 30,000 million *H. pertussis*, so that amounts could be administered in doses of 0.5 ml. each."

"Twenty-five gage, 10 to 15 mm. needles were used. Each dose of 0.5 ml. was administered deeply into alternate gluteal areas, starting with the left proximal region. To rid the needle tract of alum particles, each dose was terminated with 0.1 ml. of air. As soon as the needle was withdrawn, the site was massaged gently and briefly with sterile gauze to prevent oozing, and to distribute the alum-precipitated antigen into the deeper tissues."

"At the time of the first dose the parent was instructed to avoid excessive bed covering, to offer plenty of drinking water, to reduce the amount of food at the following meal, and to give 1 grain of aspirin one or more times daily if fever occurred. Systemic reactions were transient; occasionally the rectal temperature reached 39° C. within 4 to 12 hours after injection. It was not necessary to subdivide or delay a dose on account of severity of systemic or local reaction. The preparation was not administered during an acute infection, in prematurely born infants, in instances where the physical condition made it inadvisable, or in any child with a tendency to convulsions (such as spastics). In no instance did a child develop convulsions or show any signs of encephalopathy. . . . In some infants a residual nodule could be palpated at the time of the subsequent dose. A fluctuating or discharging alum cyst was rarely encountered—approximately once in 800 doses."

Preliminary immunity tests were not performed before the administration of these alum-precipitated antigens because in previous studies the authors had found, on the basis of immunity tests, that few infants at the age of 3 or 4 months possessed immunity to tetanus, diphtheria, and pertussis. "Passive diphtheria immunity transmitted from the mother was usually absent."

Laboratory tests and skin (Schick) tests were used as evidence of antigen-conferred immunity. "No private patient injected with this multiple antigen prepared during the past five years is known to have contracted any of these diseases. The tests were made approximately three months after the final dose of multiple antigens. In group I, a negative Schick test served as evidence for immunity to diphtheria. For tetanus, an antitoxin level of 0.1 unit or more per ml. of blood was considered evidence of adequate immunity. For pertussis, a complement fixation reaction of 3 or 4+ was considered evidence of adequate immunity. For group II, a negative Schick test and a diphtheria antitoxin level of 0.2 unit or more per ml. of blood were considered evidence of adequate immunity. The test for tetanus immunity was the same as that carried out in group I. For pertussis, the rapid agglutination test of Daughtry-Denmark was used. An agglutination reaction of 3 or 4+ was considered evidence of adequate immunity. This equals a titer 1:320 or more." The authors employed the test because they had found good correlation between it and a tube agglutination method, and the more time-consuming complement fixation reac-

tion. "When the result of a test indicated inadequate protection, a stimulating dose of 0.5 ml. of the antigen was administered; when the child was retested a month later, the immunity response was usually found to be adequate.

"Results. — Group I: Approximately three months after the final dose, follow-up tests for immunity were performed on 98 of the children, to whom three monthly doses of 0.5 ml. of the alum-precipitated mixture of diphtheria and tetanus toxoids with pertussis vaccine had been administered after the sixth month of life. The Schick test was found negative in 100 per cent; a tetanus antitoxin level of 0.1 unit or more per ml. of blood was found in 96 per cent; and the pertussis complement fixation reaction was 3 or 4+ in 83 per cent. Infants whose tests indicated inadequate protection were given an extra (fourth) dose of 0.5 ml. of the alum-precipitated mixture in the right distal gluteal area. A month later the pertussis immunity had risen to an adequate level in each of the retested children.

"Group II: Tests for immunity approximately three months following injections were performed on 163 children to whom four doses of 0.5 ml. of the alum-precipitated mixture of diphtheria and tetanus toxoids with pertussis vaccine were administered at 3, 4, 5, and 6 months. The Schick test was found negative in 100 per cent; a diphtheria antitoxin level of 0.2 unit or more per ml. of blood was found in 96 per cent; a tetanus antitoxin level of 0.1 unit per ml. of blood was found in 100 per cent; and the pertussis agglutination test showed adequate protection in 98 per cent."

Simultaneous Immunization of Newborn Infants Against Diphtheria, Tetanus, and Pertussis. Production of Antibodies and Duration of Antibody Levels in an Eastern Metropolitan Area — DI SANT'AGNESE, PAUL A. — *American Journal of Public Health*, 40: 674 (June) 1950.

"This investigation was undertaken in an effort to determine how soon after birth routine immunizations could be performed with assurance of success."

In this study, the material chosen for inoculation was a triple combined vaccine called, "Alhydrox." "In this material 20 billion *Hemophilus pertussis* organisms per ml. are added to aluminum hydroxide-adsorbed tetanus and diphtheria toxoids."

"One hundred and ninety-eight full term infants were studied. Three deep subcutaneous or intramuscular injections of the triple combined vaccine were given at monthly intervals—the first injection of 0.5 ml. at the age of 1 week, the second of 1.0 ml. at 5 weeks, and the third also of 1.0 ml. at 9 weeks of age. By the age of 9 weeks, a total of 2.5 ml. of the vaccine containing 50 billion *H. pertussis* organisms had been administered and basic prophylactic inoculation completed. A booster dose of 0.5 ml. of the same material was administered to some patients at 6 months of age, to others at the age of 1 year."

"Production of Antibodies in Early Infancy.—1. Serum Agglutinins Against *H. Pertussis* (Figure 1, A,B,E,): Before inoculation, at 1 week of age, 98 per cent of 144 newborn infants tested had no agglutinins against *H. pertussis*." At the age of 13 weeks, 1 month after the administration of the three injections of "Alhydrox," only 30 per cent of 125 patients examined had no pertussis agglutinins; 54.4 per cent had a titer of 1:400 or higher, a titer which according to several authors affords complete protection against intimate familial exposure to pertussis. "Twenty-six per cent of those tested had high agglutinin titers of 1:1,600-1:3,200.

"Four to 10 months after basic immunization, when the infants were between the ages of 6 months and 1 year, a booster dose was given. Pertussis agglutinins were titrated again 10 to 30 days after this booster dose. While the booster failed to elicit a significant change in the number of patients with 'protective' or 'high' agglutinin titers, it decreased the number of infants showing a complete absence of pertussis agglutinins from 30 per cent to 16 per cent. Antibody determination after a booster injection gives a more accurate picture of the success of immunization. Patients whose antibody-forming tissues are sensitized by the antigen, but who fail to produce circulating antibodies, may do so upon subsequent contact with the antigen.

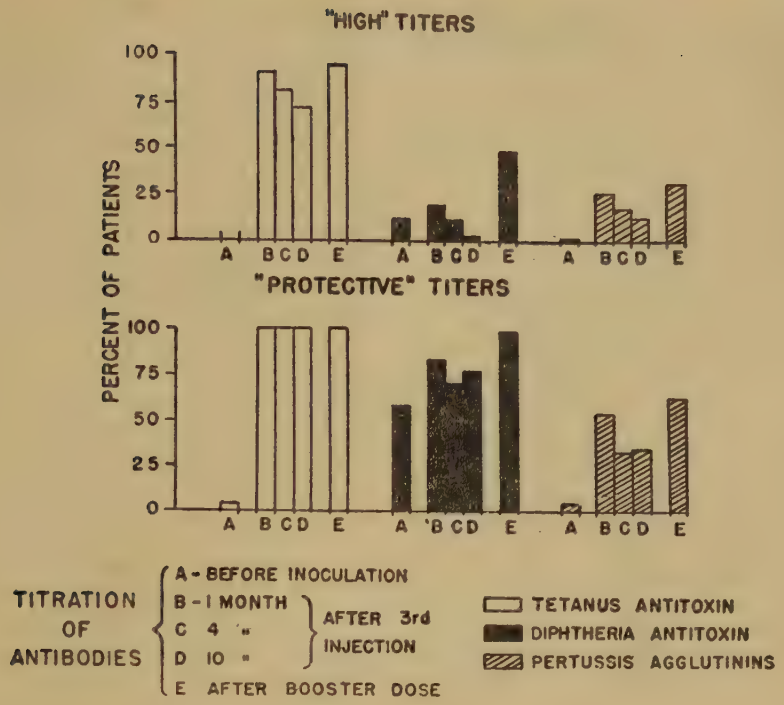

Fig. 1.—Serum Antibody Levels Before and After Administration of Prophylactic Inoculations in the Newborn Period. (di Sant'Agnese, Paul A.: *Am. J. Pub. Health*, American Public Health Association, Inc., June, 1950.)

"These figures show that the great majority of newborn infants produce antibodies against *H. pertussis* after prophylactic inoculation. Judging by some of the standards applied in the past, the percentage of infants who showed a 'protective' agglutinin titer of 1:400 or higher is rather low." Final judgment as to the degree of protection achieved will have to be postponed until more accurate standards of evaluation become available.

"2. Tetanus Antitoxin (Figure 1): Before inoculation, 15 per cent of 156 newborn infants tested had appreciable amounts of tetanus antitoxin in the serum. Tetanus antitoxin has heretofore been reported as normally not occurring in the blood of human beings." For several years in New York City, most children and adolescents going to summer camp have been immunized against tetanus. "Therefore a substantial number of young mothers must have circulating tetanus antitoxin which they transmit through the placenta to their offspring.

"At the age of 13 weeks, one month after completion of three inoculations, all of the 128 patients examined had more than the 'protective' titer of tetanus antitoxin of 0.1 unit per ml., and 92 per cent of these had very high titers of antitoxin, more than 1.0 unit per ml. of serum. As 1.0 unit per ml. was the top level tested for, no great change in titers could be expected after booster dose. These results are obviously highly satisfactory.

"3. Diphtheria Antitoxin (Figure 1): A level of 0.03 unit of antitoxin per ml. of serum was considered as affording complete protection against diphtheria. Titrations were not carried out below this level.

"Of 168 infants tested seven days after birth, 58.5 per cent were found to have 'protective' titers of antitoxin. Twelve per cent of the total had antitoxin levels of more than 1.0 unit per ml. This antitoxin was obviously transmitted by their mothers to the infants through the placenta. The crowded housing conditions and the low economic status of the families involved

may explain this relatively great number of mothers capable of transmitting passive antibodies.

"One month after the third injection 84.6 per cent of 123 infants tested had a 'protective' titer of diphtheria antitoxin, only 20 per cent had antitoxin levels of more than 1.0 unit per ml., and 15 per cent had less than the minimum antitoxin titer tested for. After booster dose, however, with 1 exception, all patients developed 'protective' antitoxin titers and the percentage of those with high antibody levels had risen from 20 per cent to 50 per cent.

"The fact that all patients except 1 had protective titers after booster dose indicates that active immunization was achieved despite the passively transmitted antitoxin present at birth in over half the cases. Even in the patients who failed to produce serum antibodies after the three basic immunizing injections the immune mechanisms had apparently been adequately 'sensitized.' It must be assumed that while part of the injected diphtheria toxoid was neutralized by circulating antitoxin, enough antigen reached the tissues to produce satisfactory immunization."

"Duration of Antibody Titers.—Levels of tetanus and diphtheria antitoxin and of serum pertussis agglutinins were determined 1 month, 4 months and 10 months after the third immunizing injection, at the ages of 13 weeks, 6 months, and 1 year (Figure 1 B, C, D), making a total follow-up period of 9 months after completion of the basic immunizing injections.

"1. Duration of Tetanus Antitoxin Titers: Throughout this period of nine months all patients examined had 'protective' titers of tetanus antitoxin. The percentage of cases with high antitoxin levels (more than 1.0 unit per ml.) decreased progressively from 92 per cent one month after completion of inoculations, to 73 per cent at the end of the first year.

"2. Duration of Diphtheria Antitoxin Titers: During the period of observation there was only a slight drop in the percentage of infants with 'protective' levels of diphtheria antitoxin, from 84 per cent at 13 weeks of age to 77 per cent at the age of 1 year. There was a steady decline, however, in the number of cases with high (more than 1.0 unit per ml.) antitoxin levels.

"3. Duration of Serum Pertussis Agglutinins: There was a decline in the nine month period of almost 50 per cent in the number of patients with serum agglutinin titers against *H. pertussis* of 1:400 or higher ('protective' titers), but no further change in the next few months. As in the case of tetanus and diphtheria antitoxin, there was a steady decrease in the proportion of patients with 'high' agglutinin titers (1:1,600-1:3,200)."

"Influence of Age on Antibody Production.—Further studies were undertaken to gage the influence of age on antibody production. A comparison was made of the results of prophylactic inoculation in the series of newborn infants under consideration with a group of older children." In all instances the same triple combined vaccine, "Alhydrox," was used following the same routine. "The only difference was in the age at which the injections were begun. While inoculations were started at 1 week of age in the newborn group, the older children were 6 months or more at the time of first injection.

"The results of the comparison are summarized in Figure 2. The group of newborn infants is assigned the filled-in blocks, and the older children the outlined ones. Only the 'high' antibody titers are considered.

"The patients in the older age group consistently showed higher pertussis agglutinin titers than the newborn infants. When analyzed with the chi square test the differences in all instances were found to be statistically significant. As passive immunity to pertussis was not present at birth, and therefore could not interfere with active immunization, the poorer antibody response of newborn infants as compared with older children must be attributed solely to immaturity of the immune mechanisms.

"Tetanus antitoxin production after inoculation was equally good in both age groups. This was presumably due to the fact that the tetanus toxoid used was of great antigenic capacity. From previous studies Alhydrox is known to have tetanus toxoid of great potency. One can assume that if a sufficiently great antigenic stimulus is given, the handicap due to immune

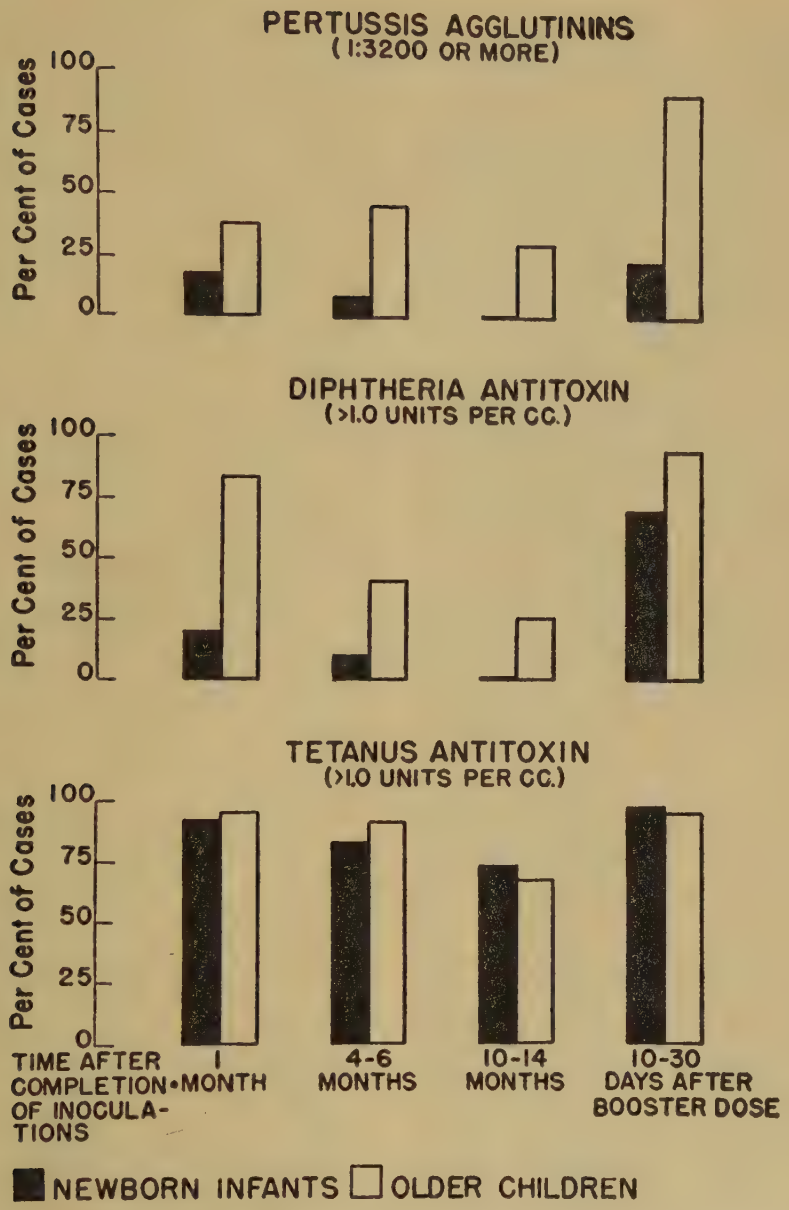

Fig. 2.—Comparison of "High" Antibody Titers Achieved After Prophylactic Inoculation by Newborn Infants and "Older" Children. (di Sant'Agnese, Paul A.: *Am. J. Pub. Health*, American Public Health Association, Inc., June, 1950.)

mechanism immaturity may be overcome and satisfactory immunization achieved.

"In the case of diphtheria, it was found that older children consistently had higher antitoxin titers after injection than newborn infants, but after booster dose the difference between the two groups was not great enough to be significant statistically. Therefore the final degree of immunization was roughly comparable in both age groups. The relatively poor initial showing of the newborn infants may be attributed at least partly to the presence of transplacentally transmitted passive diphtheria antitoxin. Here again, the antigenic stimulus of 75 Lf of diphtheria toxoid was

potent enough to overcome the combined handicaps of tissue immaturity and existing passive immunity to diphtheria."

Conclusions.—In the first months of life, antibody response to an antigenic stimulus increases with advancing age. "Another more cautious conclusion is that while the results of immunization in the very young infant may not be as good as in the older child, a significant degree of protection may be obtained by starting prophylactic injections in the newborn period. However, because of the combined handicaps of immaturity of the immune mechanisms and interference of the passive immunity to diphtheria with active immunization, it is felt that further evaluation of the degree of clinical protection afforded the individual is necessary before immunization in the newborn period is advocated as a routine procedure. It is suggested that, in the meantime, triple combined inoculation against tetanus, diphtheria, and pertussis be postponed to the age of 3 months. Thus, the critical period of immune mechanism immaturity will have been passed and immunity achieved several months earlier than by following conventional schedules."

Therapeutic Attempts with Insulin in Progressive Muscle Dystrophy of Children — MAYERHOFER, E. — *Annales paediatrici*, 174: 316 (May) 1950.

Based on Lesser's thesis that insulin causes an increase of the glycogen formation together with an increase of the sugar oxidation, the author formed the theoretic conception that in diseases of the muscles, too, insulin treatment may have a favorable therapeutic effect on the sugar metabolism and the glycogen storage of the muscle. The skeletal musculature is one of the main organs of the glycogen metabolism, if not the main organ. A quantitative balance sheet of the sugar and insulin effect shows that a large amount of sugar is deposited as muscle glycogen, and the hexose phosphoric acid of the muscle also increases appreciably under the effect of insulin (intermediary phosphorylation of the sugar). In the author's opinion both effects are favorable with respect to the muscle function. During the past year he treated 5 cases of progressive muscle dystrophy with insulin with encouraging results; although true cures were not obtained, good functional symptomatic results have been achieved. The patients gained weight, felt better and were able to get up from the sitting to the standing position without discomfort at the end of treatment. One patient who had been frail before treatment was able to walk through the room and to stay on his feet all day after treatment, while another one was able to climb stairs without trouble. True cures have not been achieved, however.

In school children the treatment consists of daily injections of small amounts of insulin; e.g., 4 to 7 units two to three times daily, together with highly sweetened tea. Intravenous glucose injections may also be used. The possibility of hypoglycemic attacks must be considered, as progressive muscle dystrophy has a definite diabetic component. In 1 case the author observed a true hypoglycemic attack after the child had eaten less than usual for more than a day. The diet during insulin treatment should be rich in flour and sugar, and when this precaution is taken adverse results of the insulin treatment do not occur. In smaller children only 2 to 3 units of insulin are given two or three times daily.

One writer used a combination of insulin injections with pancreatic extracts perorally and reported complete cure in 18 cases after six months. Another treated 14 cases with insulin and obtained various degrees of improvement in 9 of them while 5 proved refractory. The ununiform results were attributed to differences in the type of affection, duration of the process, general condition and other factors.

In his fundamental work in 1891 one writer stated that progressive muscle dystrophy constitutes a special trophoneurosis of the muscle, and the author accepted the trophoneurotic character of this disease for the following reasons: First in many of his cases the trophic or better atrophic component predominated in the clinical syndrome and the trophic phenomena largely resembled those observed by pediatricians in gastrointestinal decomposition, and second the conception of a trophoneurosis or some alimentary-pathogenetic etiology gives more hope and opportunity to institute effective treatment.

Muscle dystrophy was attributed by one writer to a sympathetic damage and he

introduced adrenalin treatment; the latter has been said to be capable of transforming progressive into nonprogressive dystrophy. Adrenalin and insulin are antagonists and the transitory hyperglycemia provoked by adrenalin leads to a secondary increase of the insulin production so that the adrenalin treatment may correspond to an indirect insulin treatment.

The results of adrenalin treatment could be improved by combination with pilocarpine injections although some authors reported no or only little effect of this treatment. In advanced cases, particularly when the muscle fibers are already atrophic and replaced by connective tissue and fat, no improvement can be expected from adrenalin or any other drug.

Amino-acetic acid treatment was introduced on the basis of the conception of a diminution of the amino-acetic acid contents of the organism in this disease, caused by a primary disturbance of the creatine metabolism. The creatinine content of the muscle is said to be extremely low in progressive dystrophy and it may be assumed that the diseased muscle is unable to form and to store creatine normally. Contrary to the normal muscle the diseased one is unable to utilize orally administered creatinine. With amino-acetic acid treatment the creatinine excretion is increased, and apparently the diseased muscle can synthetize creatine from amino-acetic acid, but is unable to retain and store it in the form of the anhydride creatinine. However, after several weeks of amino-acetic acid treatment the urinary creatine excretion falls to the initial value or even lower, while the creatinine excretion increases, so that the creatine-creatinine metabolism seems to become more nearly normal. The creatine tolerance increases during treatment so that later on artificially administered creatinine is largely retained in the body. The muscle concentration of creatine and total nitrogen increases. Thus the amino-acetic acid may exert an indirect favorable effect on the diseased muscles. A particularly illustrative example concerned a physician who suffered from progressive muscle dystrophy and who felt better with amino-acetic acid treatment than with any of the other methods he had tried before. It is believed that he had come close to a causal treatment. The author treated 15 cases and observed improvement but never as convincing as in the case of the physician mentioned above.

Roentgenotherapy has also been tried successfully, particularly in initial cases. While the carbohydrate metabolism is undoubtedly of great significance in progressive muscle dystrophy the disease cannot be explained on this basis alone. While older authors denied endocrine disturbances such disturbances have been given increasing consideration lately. A low blood sugar level has been found, and a disturbance of the endocrine correlations with an increased carbohydrate tolerance has been assumed. One writer assumed that the pituitary gland is of particular significance and that its extracts have therapeutic value. Clinical endocrine syndromes observed in progressive muscle dystrophy include genital hypoplasia, exophthalmos, hypoplasia or hyperplasia of the thyroid gland, myxedema, osteomyopathies and general infantilism. Sympathetic disturbances may also lead to endocrine disturbances.

The author observed a case of progressive muscle dystrophy with abortive acrodynia and definite granulosis rubra nasi, the latter constituting a not infrequent associated symptom of vegetative-nervous affections of Feer's type; concomitant endocrine symptoms are rather frequent in Feer's disease. The author also observed cases of progressive muscle dystrophy with a reduction of the blood lipase and trypsin levels, with diabetes-like symptoms, with tendency to hypoglycemic collapse after insulin injections and with a large protruding tongue as in myxedema; all these observations indicate a direct or indirect participation of various endocrine and other glands in the process.

According to recent work a disturbance of the myohemoglobin metabolism is also demonstrable and may be found to a lesser extent in family members of the patient who do not show any manifest signs of the disease; the supervening of an endocrine pancreatic functional disturbance would then lead to clinical manifestation of the previously latent myopathy. Glycogen formation in the skeletal muscle after insulin injection has been demonstrated experimentally; even in trit-

urated surviving muscle, addition of insulin leads to an increase of the glycogen. Peroral administration of yeast preparations is claimed to have a favorable effect on the glycogen deposits in liver and muscles, particularly when at the same time an effect on the muscle glycogen is produced by suitable exercise. A not inconsiderable increase of the efficacy of the muscle could be found on functional studies with minute insulin amounts (0.005 to 0.02 units per cc.). The glycogen formation in the muscles is also favored by caffeine, atropine, acetylcholine and creatine, according to one writer the presence of creatine is indispensable for the normal glycogen level of the muscles.

Insulin has an excellent effect in progressive muscle dystrophy of children, particularly in recent cases in which definite muscle atrophy and local pseudohypertrophy are absent. The effect of insulin is based on the increased formation and storage of glycogen and a better regulation of the glycogen consumption in the muscle itself. A real cure of the disease is not achieved, however, with this treatment.

Antirheumatic Activity of Ascorbic Acid in Large Doses. Preliminary Observations on 7 Patients with Rheumatic Fever—Massell, Benedict F., Warren, Joseph E., Patterson, Paul R. and Lehmus, Harold J. — *New England Journal of Medicine*, 242: 614 (April 20) 1950.

The writers present observations suggesting that ascorbic acid possesses antirheumatic activity when administered in large doses. "Because of the small number of patients treated so far, the relatively short period of follow-up study and the well known variability of rheumatic fever even when it is uninfluenced by therapy, the present communication must be considered preliminary in the strictest sense of the word."

"Since January 2, 1950, ascorbic acid has been given by mouth in doses of 1 Gm. four times daily (total of 4 Gm. per day) for periods varying from 8 to 26 days to a total of 7 patients with rheumatic fever. There has been a follow-up period of 12 days to two months in 3 patients in whom therapy has been discontinued; at the time of this writing, March 20, 1950, 4 patients are still receiving treatment.

"The results of treatment with ascorbic acid can best be presented by a brief description of the clinical course of each of the 7 patients:

"Case 1.—P. L. is a 13 year old boy whose pertinent findings prior to treatment included migratory polyarthritis, a temperature of 101° to 102° F. by rectum and elevation of the sedimentation rate. His heart seemed normal except for a slight systolic murmur. Ascorbic acid was given for a total of 8 days (January 2 through January 9, 1950). Within 24 hours of the beginning of treatment the joint manifestations had disappeared, and the fever had lessened. The temperature remained normal after the second day of therapy, but the sedimentation rate continued to be elevated.

"Case 2.—R. M. is a 14 year old boy who has suffered for many months from persistent rheumatic fever, severe cardiac involvement and chronic hepatic congestion. Ascorbic acid therapy was begun on February 4, 1950, during a period of increasing rheumatic activity (possibly just a rheumatic fever cycle), manifested by temperature elevation to 102° F. by rectum, rise in the sedimentation rate and increased congestion of the liver. The fever began to lessen on February 5, and the temperature has remained normal since February 6. The size of the liver has not changed appreciably, and the sedimentation rate is still elevated. Ascorbic acid was given for a total of only 8 days.

"Case 3.—E. T. is a 15 year old boy who for six weeks prior to therapy had been ill with migratory objective polyarthritis, fever, sinus tachycardia and a rapid sedimentation rate. Except for a slight systolic murmur, his heart seemed normal. With ascorbic acid therapy, which was given for a total of 15 days (February 21 to March 7, 1950), there was prompt improvement in symptoms and reduction in fever. Since the second day of treatment the temperature has been entirely normal, and there have been no symptoms or signs referable to the joints. By March 20 the sedimentation rate had fallen to within normal limits.

"Case 4.—W. D. is a 14 year old boy with rheumatic heart disease whose symp-

toms of rheumatic fever had been controlled by acetyl salicylic acid. However, after the omission of this drug and prior to treatment with ascorbic acid he had elevation of the temperature to 102° F. by rectum, several nosebleeds and a swollen painful knee. Ascorbic acid therapy was begun on February 22, 1950, and continued to the present time. Improvement was definite but gradual over a 4 day period. He has been symptom free and afebrile since February 26. The sedimentation rate has fallen from an initial level of 1.4 to the slightly elevated level of 0.55 mm. per minute.

"Case 5.—R. F. is an 11 year old girl who, on admission to the hospital on March 6, 1950, was obviously acutely ill with active rheumatic fever, pancarditis and congestive heart failure. Pertinent findings included a temperature of 104° F. by rectum, tender, swollen finger joints, a respiratory rate of 60 to 75, cardiac enlargement, murmurs of mitral regurgitation and aortic regurgitation, nodal rhythm, a ventricular rate of 160, a pericardial friction rub, marked enlargement and tenderness of the liver, and edema of the legs and lower back. Treatment with ascorbic acid was begun on the evening of March 6. The fever and joint symptoms gradually lessened and have been completely absent since March 13. The friction rub has not been audible since March 10. The cardiac rhythm reverted to normal within 24 hours of therapy, and the heart rate is now about 120. Hepatic congestion and peripheral edema have entirely disappeared. The patient now feels well and appears obviously much improved. The sedimentation rate is still elevated.

"Case 6.—A. F. is an 18 year old boy without cardiac involvement whose rheumatic fever manifestations just prior to ascorbic acid therapy (given from March 7, 1950, to the present) consisted of elevation of the temperature to 101° F. by rectum, objective polyarthritis and elevation of the sedimentation rate. Treatment was followed by somewhat slow but steady improvement. The temperature has been normal since March 10, and the joint manifestations have remained completely subsided since March 11. The sedimentation rate is still elevated.

"Case 7.—P. B. is a 5 year old boy with known rheumatic heart disease who had a recrudescence of rheumatic fever on March 8, 1950. Manifestations included elevation of the temperature to 104° F. by rectum, sinus tachycardia, pallor and pain and tenderness of the right knee and both ankles. The joint symptoms subsided spontaneously prior to treatment, but the high fever continued. Ascorbic acid therapy was begun on March 14. Since that time there has been a steady decline in temperature, and fever has been entirely absent since March 17. The heart rate has slowed, and the patient's appearance has greatly improved."

Although observations suggest that ascorbic acid when administered in sufficient amounts possesses antirheumatic activity, no final assessments can yet be made regarding the possible therapeutic value of this substance.

The Influence of the Birth Weight on the Mental Development of the Child — SCHACHTER, M. AND COTTE, S. — *Pediatrie*, 39: 359, 1950.

From the authors' study on the influence of the birth weight on the mental development of the child, prematures were excluded; the authors' material is derived from a more or less impaired population, and similar studies on a child population in good health would seem desirable. English authors recently studied the influence of the birth weight on the somatic development and found a constant parallel correlation but they did not include the mental development. One writer studied the influence of the birth weight on the mental development, and without giving many details, mentioned a correlation; the intelligence quotient of the infants with a birth weight of above 4,500 Gm. would be higher than that of those with a birth weight between 2,500 and 3,000 Gm. (108.8 as compared to 105.2). The authors' studies were made on 899 boys and 486 girls, and the Binet-Simon test was carried out at least once in each case. Among the parents of these children more than 20 per cent were alcoholics, about 8 per cent suffered from tuberculosis, about 6 per cent from syphilis, and about 4 per cent suffered from mental diseases or antisocial reactions. Forceps deliveries amount-

ed to 109 or 7.87 per cent, 208 infants or 15.01 per cent were born asphyctic, early or later convulsions occurred in 129 cases or 9.31 per cent, and maternal gestoses amounted to 20 cases or 1.44 per cent. The Binet-Simon test revealed a normal condition in 362 cases, a satisfactory condition in 337 cases, a borderline condition in 229 cases, slight, moderate and profound debility in 147, 84 and 71 cases respectively, imbecility in 145 cases, and idiocy in 19 cases. Thus more than one third of the children showed oligophrenia of variable importance, and the incidence of imbecility was 10.45 per cent, illustrating the cerebrogenic nature of the oligophrenia in this material. Arbitrarily the material was divided into the following birth weight classes: less than 2,000 Gm., 28 cases or 2.02 per cent; between 2,000 and 3,500 Gm., 801 cases or 57.68 per cent; between 3,500 and 4,500 Gm., 466 cases or 33.64 per cent; above 4,500 Gm., 90 cases or 6.49 per cent.

A normal mental level was found in 17.85, 25.09, 29.82 and 18.88 per cent of the infants of these four weight groups respectively; thus the mentally most favored groups were the second and third; that is, the ones with the most physiologic birth weight. A satisfactory level was found in 14.28, 24.21, 24.67 and 26.66 per cent respectively; thus this level of slight diminution of the mental development was most frequently found in the heavier infants.

The borderline mental level was found in 28.56, 17.22, 14.59 and 16.66 per cent respectively; this group shows the first pathologic symptom; namely, the fact that a lower than normal birth weight may be an unfavorable factor for later mental development.

Slight debility was found in 10.71, 10.11, 10.08 and 17.77 per cent respectively, showing that an abnormally high birth weight may be an unfavorable factor.

Moderate debility was found in 10.71, 5.86, 5.36 and 10.00 per cent respectively, showing a definite unfavorable effect of both abnormally high and abnormally low birth weight.

Profound debility was found in 0.00, 5.86, 5.36 and 0.00 per cent; that is, not at all in the abnormally high and abnormally low weight groups.

Imbecility was found in 10.71, 10.98, 9.65 and 10.00 per cent respectively; in this group the cerebral factor played the most important part and the birth weight had only a secondary effect.

Idiocy was found in 7.14, 0.62, 0.64 and 0.00 per cent respectively; thus the abnormally low birth weight seemed to have an unfavorable effect.

Taking the virtually normal mental levels together they were found in 69.08, 66.52, 62.20 and 60.69 per cent, thus decreasing with increasing birth weight. The oligophrenic levels were found in 39.31, 37.80, 33.48 and 30.92 per cent respectively, indicating that oligophrenia had the lowest incidence in the physiologic weight group.

In conclusion, a significant but not very marked correlation was found between birth weight and subsequent mental development, measured by the Binet-Simon test.

Clinical Observations on a New Sulfonamide (Gantrisin) — BIGLER, JOHN A. AND THOMAS, ORVILLE — *American Journal of Diseases of Children*, 79: 785 (May) 1950.

"Gantrisin, 3,4-dimethyl-5-sulfanilamido-isoxazole, formerly known as NU-445, is a new sulfonamide which has as its advantages a high degree of solubility and low toxicity. Because of its solubility, there is no crystallization in the urine except with doses that are much higher than would be used therapeutically."

"Because of the high rate of solubility and the low incidence of toxicity, this sulfonamide preparation was used alone in the treatment of 71 children . . . . with various types of infections. . . . The response was excellent in all but 7 patients. Of the latter, 3 were thought to have atypical pneumonia, 1 nonhemolytic streptococcus pyuria, 1 rheumatic fever, 1 infectious mononucleosis and 1 exanthema subitum."

"Lobar Pneumonia.—The ages of these patients were from 10 months to 10 years. At the onset of therapy the temperatures were 102 to 105 F. These returned to normal in 24 to 48 hours and remained so.

"Bronchopneumonia.—The temperatures of these 6 patients, aged 2 to 5 years, were 102 to 104 F. when administration of the

drug was started and became normal after 24 to 48 hours.

"Atypical Form of Pneumonia.—Two of these children, both 10 years of age, had what appeared to be a virus pneumonia, with a temperature of 105 F. in 1 and of 103 F. in the other. The white blood cell counts were 10,000 in both children, and the roentgenograms, physical findings and clinical courses were suggestive of the presence of a virus infection. Both showed no improvement after three days of Gantrisin therapy, with blood levels of 12.7 and 10.2 mg. per hundred cubic centimeters. They were given penicillin, 30,000 units, every three hours intramuscularly. With this therapy the temperature returned to normal in six days in 1 child and in three days in the other, indicating little effect with penicillin.

"The third patient was a 5 year old boy who had no fever but who had a pulmonary consolidation which was thought to be tuberculous in origin. He had had a recent positive Mantoux reaction. The drug was used for three days with no improvement in his condition. The blood level of the drug was 6.4 mg. per hundred cubic centimeters. Smears of gastric washings and guinea pig inoculations were negative for tubercle bacilli. The patient was discharged from the hospital after three weeks with no change in his pulmonary findings.

"Bronchitis.—There was clinical and physical evidence of pulmonary infection but negative roentgenographic findings in 8 patients. These 8 children, ages 13 months to 5 ½ years, had temperatures of 101 to 102 F. at the onset of therapy. They became normal in 24 to 36 hours.

"Otitis Media.—Eight children, 7 month to 6 years of age, had temperatures of 102 to 105 F. at the time medication was begun. The other child with acute otitis media had a normal temperature during the entire course of his illness. The elevated temperatures returned to normal in 24 to 48 hours. Paracenteses were not performed. Suppuration was present in 3 children before the institution of therapy and subsided within one week.

"Tonsillitis.—All the 19 children had moderate to severe infection of the tonsils or the throat. The ages varied from 9 months to 11 years, with temperatures of 101 to 105 F. at the start of therapy. These patients were free of fever in 12 to 24 hours.

"Adenitis.—There were 2 children with inguinal adenitis, 2 with cervical adenitis and 1 with axillary adenitis. The nodes were large and tender. The ages of the patients were 2 to 9 years, and their temperatures were 101 to 102 F. The temperatures returned to normal in 12 to 36 hours, with complete subsidence of the infection without suppuration or surgical intervention in 4 of the children. Surgical incision was necessary in 1 child with cervical adenitis.

"Urinary Tract Infections.—Three children in this group, aged 2 to 5 years, with temperatures of 101 to 104 F., had rapid subsidence of both fever and pyuria. Urine cultures became negative for pathogens. In the fourth patient, Gantrisin was used without effect on an infection due to a nonhemolytic streptococcus.

"Miscellaneous Infections.—These consisted of an alveolar abscess in a 10 year old child with a temperature of 101 F., acute bursitis with heat and redness in a 9 year old boy without fever, an extensive infected burn in a 6 year old child with a temperature of 103 F., an undetermined infection in a 5 ½ month old infant with an esophageal atresia and a temperature of 103 F. and pneumococcic dacryocystitis in a 6 month old infant. The temperatures remained normal after 24 to 48 hours of therapy. One child with infectious mononucleosis, 1 with rheumatic fever and 1 with exanthema subitum did not show any response.

"Approximately 50 other infants and children have also received Gantrisin in combination with penicillin and streptomycin. In 4 of these children being treated for influenzal meningitis with streptomycin and sulfadiazine, blood appeared in the urine within 24 to 48 hours. Administration of the sulfadiazine was discontinued, Gantrisin was substituted and its use was continued for two weeks. The red blood cells disappeared from the urine and normal recovery occurred.

"Cultures.—Cultures taken on this group of children showed no variations from those of other children seen at the same time but being treated with other drugs."

"Dosage.—The Gantrisin was supplied in 0.5 Gm. tablets for oral administration.

The usual dosage was 1 to 1 ½ grains per pound (0.13 to 0.19 Gm. per Kg.) of body weight divided into four to six doses daily. A few children were given as much as 2 grains per pound (0.26 Gm. per Kg.). The initial and sometimes the second dose was doubled on the first day of therapy. Administration of the drug was continued for 3 to 10 days. No alkali was given. In no instance was there a recurrence of the infection."

Reactions.—In the combined group of the 71 patients and 50 other children no reactions were present that could be attributed to the drug. "One child with lobar pneumonia and a temperature of 104 F. took the drug poorly the first few days. In another there was some nausea the third day but no vomiting. Crystalluria and hematuria did not occur. There were no changes in the red blood cell count or in the hemoglobin concentration. In no instance did a leukopenia develop, although in the 9 year old boy with inguinal adenitis, lymphangitis of the leg and a temperature of 102 F., the white blood cell count was 3,000, with 40 per cent polymorphonuclear cells and 60 per cent lymphocytes, 24 hours after his admission and the start of therapy. Unfortunately, another count was not obtained before his discharge. It was felt that the leukopenia occurred with his infection rather than with the administration of the drug. No secondary rise of temperature occurred during medication up to 10 days.

"Blood Levels.—With the usual dosage of 1 to 1 ½ grains per pound daily, the blood levels varied from 3 to 15.7 mg. per hundred cubic centimeters. The average blood level was 6.4 to 10.7 mg."

Treatment of Lead Encephalopathy with BAL (2.3-Dimercaptopropanol) — Ennis, Julius M. and Harrison, Harold E. with the Technical Assistance of Evelyn Fleishman — *Pediatrics*, 5: 853 (May) 1950.

"This study reports observations on 16 children with lead encephalopathy admitted to four Baltimore hospitals within the past three years and treated with BAL. During the previous five years, 1943 through 1947, over 200 children seen at these hospitals were diagnosed as suffering from lead poisoning. Of these, 31 cases had neurologic signs and symptoms of sufficient severity to justify a diagnosis of lead encephalopathy. This group of 31 children constitutes the control for the treated series. The age distribution was approximately the same in control and BAL-treated groups. The patients in the control group were treated by a variety of methods including the administration of citrate and phosphate salts. In order to be able to compare results in the two series, the cases were divided into two groups according to severity. The diagnosis of lead poisoning was based on the findings of either roentgenographic evidence of heavy metal deposition at the ends of the long bones, or an elevation of the level of lead in the blood above 0.05 mg./100 Gm. blood, in children with a history of pica and presenting symptoms or signs such as vomiting, anemia, abdominal pain, anorexia and constipation. A child with lead poisoning was considered to have encephalopathy if he showed one or more of the following manifestations: convulsions, increased intracranial pressure, persistent vomiting, marked personality change, cranial nerve palsies, muscle weakness or paralysis, ataxia, drowsiness and increased concentration of protein or pleocytosis in cerebrospinal fluid. The encephalopathy was classified as severe if the patient had repeated convulsions which were difficult to control or stupor or coma which persisted for longer than would be consistent with the usual postconvulsive state; i.e., over 12 hours. Using these criteria, 18 of the 31 cases of lead encephalopathy in the control group were classified as severe and 13 as mild. Of those treated with BAL, 9 were severe and 7 mild."

"The signs, symptoms and laboratory findings in both control and treated groups were similar to those reported by other writers. A history of pica could be elicited in almost every case and the most common source was found to be painted woodwork and painted plaster. An elevated blood lead concentration was found in every case, and the typical zone of increased density at the end of the long bones was seen in all but 1 of the cases in which roentgenographic examination was done. Urinary abnormalities were noted in more than half of the group. Anemia, indicated by a concentration of hemoglobin

of less than 10 Gm./100 cc. blood, was present in almost all cases, and there was a high incidence of concurrent or preceding infection.

"BAL was injected intramuscularly as a 10 per cent solution in benzyl benzoate and oil. The initial dosage was 2 mg./Kg. body weight every 4 hours for 4 injections, and the dose was increased first to 3 and then 4 mg./Kg. body weight/injection given every 4 hours for 10 days. Several cases received shorter courses of treatment. No severe toxic effects were noted with this dosage, but in several instances vomiting occurred within an hour of each intramuscular injection. In none of these cases was it thought necessary to discontinue therapy."

"In the BAL-treated group, 2 of 9 severe cases died, compared with a mortality of 12 out of 18 severe cases in the control group. There were no deaths resulting from 'mild' lead encephalopathy in either BAL or control groups.

"All the 7 children recovering from severe lead encephalopathy in the BAL-treated series have been kept under observation in outpatient departments for periods varying from three years to two months. Two have been too recently discharged from the hospital to be evaluated, but appear to have no neurologic residua. One, who was hospitalized a year ago at the age of 18 months, is apparently well at the present time, although he has not been submitted to psychometric examination. The remaining 4 children have had recurrent convulsions which are at present satisfactorily controlled by anticonvulsant therapy. One child is obviously mentally retarded and has an I.Q. of 62. She presents behavior difficulties of a serious enough nature to be of concern to the parents. The other 3 were thought to be normal or only slightly retarded. However, on testing, they were shown to have I.Q.'s of 79, 78 and 69. This last child was improving rapidly at the time of the test which was performed only four months after discharge, and it was thought that there might be an increase in I.Q. at a subsequent examination. In 1 patient, pneumoencephalography revealed a dilated right ventricle and right-sided cerebral atrophy. There were abnormalities in the electroencephalographic records of 3. Three of the 4 are restless and distractible. None of the survivors is deaf or blind, or so severely retarded as to require institutional care.

"Six surviving children with severe encephalopathy in the control group have been followed. Five were found to show severe mental retardation and 1 was only mildly defective. Three presented the problem of marked personality difficulties. One was deaf and blind, and another was blind.

"Two of the 7 patients with 'mild' lead encephalopathy treated with BAL have had recurrent convulsions successfully treated by anticonvulsant drugs. One of these children was severely retarded before hospitalization and has remained so. The remaining 5 have no detectable neurologic residua, although psychometric examinations have not been done. Of the 9 children with 'mild' encephalopathy in the control group, 2 showed no residua, 5 were considered retarded and 2 had recurrent convulsions."

"The concentration of blood lead in each case fell during hospitalization irrespective of type of treatment, and the rate of fall appeared to depend on the original concentration. One of the highest concentrations of blood lead (.51 mg./100 Gm. blood) was found in a patient without marked signs or symptoms of lead intoxication who was investigated for lead poisoning because of a profound anemia found following admission to the hospital for another disease. Although he was not treated with BAL, the blood level fell from 0.51 to 0.18 mg./100 Gm. blood in 10 days."

The effect of BAL on the urinary excretion of lead was studied in 6 cases of encephalopathy. "In each case, the concentration of lead in the urine rose with treatment, with return to pretreatment levels in some cases during the period of treatment. One of these patients was readmitted 6 months after recovery from severe lead encephalopathy and given an 11 day course of BAL therapy. On this occasion, the urinary lead level rose again, the rise persisting for the duration of BAL administration. The concentrations of lead in the urine in a similar patient not given BAL were relatively constant on three consecutive days. BAL was given for three days to another patient recover-

ing from acute encephalopathy. The urinary lead level was 0.5 mg./l. urine before administration of BAL and 1.3 mg./l. urine after three days of BAL administration."

"Conclusions.—BAL is apparently effective in lowering the mortality rate in children with severe lead encephalopathy. The severity of the residua of severe lead encephalopathy may also be reduced by BAL treatment. No conclusive effects of therapy could be demonstrated in subacute mild cases of lead encephalopathy. The toxic effects of BAL in this series have been limited to nausea and vomiting which were never severe enough to contraindicate continuation of treatment. There was no evidence of exacerbation of symptoms in mild cases of lead poisoning treated with BAL."

Blood Transfusions in Pediatrics — BIANCALANA, ARTHUR—*Anais paulistas de medicina e cirurgia*, 59: 120 (February) 1950.

The indications for blood transfusions are enumerated as follows:

1. Medical hemorrhages caused (*a*) by hypoprothrombinemia in which the transfusion furnishes the lacking prothrombin, (*b*) by thrombocytopenia in which case thrombocytes are furnished and (*c*) hemophilia in which case the so-called antihemophilic factor is furnished.

2. Surgical hemorrhages in which not only the elements for improved coagulation are furnished but also the blood volume is restored.

3. Blood diseases such as (*a*) fetal erythroblastosis in which the transfusion will furnish the blood necessary for repair of the anemia from hemolysis and which will increase the means of defense and prevent complications and sequelae, (*b*) primary anemia of the newborn of an idiopathic type in which erythrocytes are needed and permit ready cure, (*c*) congenital hemolytic anemia with microspherocytosis; in this case, care is needed in transfusions during the hemolytic stage as the presence of irregular agglutinins may aggravate the syndrome, and plasma should be used until the irregular agglutinins disappear, correcting the anemia with erythrocyte transfusions later on, (*d*) acute erythroblastic hemolytic anemia of Lederer's type, of infectious origin and associated with hepatosplenomegaly; in this case the transfusion is not only a substitutive measure but also helps combating the infection itself, (*e*) Cooley's anemia and von Jaksch's anemia which is of a pseudoleukemic character and of a fatal prognosis in spite of improvements after transfusions, (*f*) chronic hemolytic anemia with nocturnal paroxysmal hemoglobinuria (Marchiafava-Micheli), (*g*) deficiency anemias (iron deficiency, malnutrition and worm infestation), (*h*) megaloblastic anemia, (*i*) congenital or toxic aplastic or hypoplastic anemia, (*j*) leukemia, Hodgkin's disease, cancer and other diseases in which transfusions will prolong life and permit the use of drugs aiming at temporary or definite cure.

4. Infections in which organic defenses are improved and globular destruction is repaired to a certain extent.

5. Congenital debility.

6. Poisonings in which the erythrocytes are normal in number but have lost their capacity to carry oxygen as carbon monoxide, sulfonamide and thiouracil poisoning.

7. Preoperatively and postoperatively for diminution of the surgical risk.

8. Nutritional affections like dystrophy, dyspepsia, toxicosis and dehydration in which plasma transfusions may have miraculous effects.

9. Prematurity with loss of weight, in which case, plasma transfusions are helpful.

10. Burns.

11. Traumatic shock.

12. Nephroses.

Generally speaking, there are no contraindications to blood transfusions, but in certain cases of heart failure, and according to some authors in acute leukemias, reactions are frequent and may produce a fatal aggravation of the condition.

The amount of blood to be transfused is mostly determined empirically rather than on a definitely established scientific basis, and the same applies to the speed of transfusion. The author uses the following criteria: In medical hemorrhages the amount is based on the total blood volume the child should have (1/13 of the total weight) and the blood count and hemoglobin concentration. In surgical hemorrhages and blood diseases the same computation is used, but if the hemorrhage persists the

loss must be compensated. In infections small amounts of 50 to 100 cc. may be transfused repeatedly during the day. In toxicoses, dehydration, acute and chronic dyspepsia, burns, nutritional edema and nephroses, cases with hemoconcentration require 50 cc. for each point that the hematocrit value exceeds 36 per cent in infants and 40 per cent in older children; dilution with saline solution will be beneficial in order to secure hydration, and up to 1,000 cc. may be given of the saline solution under strict control for appearance of pretibial edema, and pulmonary stertors in order to avoid cardiopulmonary complications. In cases with hemodilution or possibly edema, normal, or even better, concentrated plasma is used, the more concentrated, the lower the hematocrit reading. Regression of edemas and reestablishment of the hematocrit value will indicate when to suspend transfusions. In shock, transfusion should be done as rapidly as possible until the patient improves and the symptoms regress; in other cases the speed should not exceed 4 cc. per minute and the child should be watched constantly, particularly in cases of marked dystrophy and in cardiac cases with imminent failure. The tolerance of children to transfusion varies widely, and 300 to 700 cc. of blood have been given over a period of two to four hours to children aged 6 with good tolerance, while fatal complications resulted in others from 20 to 50 cc. of plasma or whole blood. The deciding factors in this respect are speed, rigorous observation, environment and condition of the liver; the author recommends a special well equipped room for transfusions in children and constant supervision by a specialist.

The intraperitoneal approach was suggested in 1878 but may lead to serious complications and does not give certainty of absorption which is slow and takes place through the lymphatics. The intracardial approach may be useful in very exceptional cases, as in generalized third degree burns. The upper longitudinal sinus is easily accessible but transfusion into it may cause serious and often fatal complications similar to speed shock, with a cerebral hematoma found on autopsy. Therefore, most authors have given up this method, but the author believes that with proper technic it may be very valuable in certain cases and should not fall into complete disuse. The veins are most commonly used and an experienced operator will almost always be able to find a vein amenable to introduction of a needle even in infants. The superficial veins are easier to control although of smaller caliber. A well placed cuff is important and care should be taken to preserve arterial pulsation below the cuff. Short-beveled sharp platinum needles are preferably used. Exceptionally in acute dysentery, toxicosis or shock the veins may be collapsed and then the medullary approach may have to be used and will prove highly satisfactory. The arterial approach is difficult to handle and the author never had to use it in children. The bone marrow is frequently used for introduction of blood and its derivatives, particularly that of the long bones, and immobilization of the child for long periods of time is easier with this approach. The most frequent complication is represented by osteomyelitis; among 800 children the author observed this complication in 3, all of them in a precarious general condition. The osteomyelitis responded well to antibiotic treatment in 2 of these cases, while the third child developed chronic osteomyelitis. The author recommends the medullary approach only if the veins cannot be entered or if the transfusion is to be kept up for long periods of time (12 to 24 hours or more). No anesthesia is required for medullary puncture. Direct transfusion is suitable only for older children with good veins as it must be done rapidly in order to avoid coagulation; it has the disadvantages of greater circulatory overloading, late hemolytic reactions, and venous embolism. The indirect method most frequently uses the following three types of apparatuses; namely, pressure injection through a large Erlenmeyer flask, syringes of 100 to 200 cc. capacity, or the gravity method. In infants the epicranial veins may be used successfully without special fixation; in older children the head must be fixed in the lateral position.

Particularly for newborns and infants a special room with an adequate temperature, humidity and oxygen content of the air is important, and equipment for handling of complications must be ready.

In 92 per cent of the cases of fetal erythroblastosis the mother is found to be Rh-negative and the infant Rh-positive, while in 6 per cent both are Rh-positive, but the mother is Hr-negative and the infant Hr-negative and anti-Hr agglutinin is found in the maternal serum. Finally in some cases Rh or Hr sensitivity can be ruled out completely and sensitization must be attributed to A and B agglutinogens present in the fetus. In cases with intense progressive anemia and marked progressive jaundice immediately after birth exsanguination-transfusion with Rh-negative blood or lavaged maternal erythrocytes is indicated. In cases with moderate anemia (around 3 million erythrocytes), discrete jaundice and slow postpartal development transfusions with Rh-negative blood are indicated until the blood picture is stabilized and the jaundice is controlled. In cases with slight anemia (more than 4 million erythrocytes), slight jaundice and a very slow course with a tendency to spontaneous normalization expectant treatment may be used or some small transfusions with Rh-negative blood may be given. Some authors advise such transfusions regardless of the degree of anemia. The goal of transfusions in fetal erythroblastosis is the substitution for erythrocytes destroyed during the hemolytic crisis which generally lasts up to two to three weeks after birth.

In exsanguination-transfusion the use of half of the total blood volume of the infant will correspond to withdrawal to 39.4 per cent of the infantile blood; the percentage values of withdrawal for the use of one, two and three times the total blood volume are 63.2, 86.5 and 95.0 per cent respectively, and the use of two times the total blood volume seems optimal; Rh-negative blood of the same blood group, or blood of group O from which the agglutinins have been absorbed by Witebsky's substance must be used. In order to be effective the procedure must be rapid, not consuming more than an hour. One writer described a simplified modification of Diamond's method; a Nélaton sound is introduced into the umbilical vein, and with a 10 cc. syringe 10 cc. of blood are injected and the same amount is withdrawn after a few seconds; the procedure is repeated until double the infant's blood volume has been used. Heparinization of the infant is not resorted to, but paraffined syringes constantly lavaged with saline solution are used in order to prevent coagulation. This method can be used only during the first 24 hours of life as later use of the umbilical vein is difficult and even dangerous. After the first day of life the author uses Wiener's technic with heparinization of the infant. The radial artery is dissected for blood withdrawal and a needle is introduced into it or it is simply divided; one of the veins is also dissected for the infusion (internal saphenous vein). First 100 cc. of blood are transfused, and then 100 cc. are withdrawn while another 100 cc. are transfused; this is repeated until double the total infantile blood volume has been transfused. The total blood volume is considered to be 1/13 of the total weight. Thus about 85 per cent of the blood is substituted and an excess of 100 cc. of blood is given. If indicated exsanguination-transfusion should be done as early as possible in order to avoid the neurologic sequelae of fetal erythroblastosis; Coombs' test should be used for early diagnosis.

The author deals only with complications of blood transfusions which have a different or peculiar character in children. The immediate complications are the most serious ones and occur almost exclusively in children in a precarious general condition; they are attributable to mechanical factors; namely, the sudden increase of the blood volume in an organism which does not rapidly adapt itself to the changed circulatory conditions. A less alarming immediate reaction is the allergic one; if only the skin is involved and the reaction is not intense the transfusion may be continued after antiallergic medication, but if the mucous membranes are chiefly involved the transfusion must be discontinued and effective antiallergics like calcium, sodium thiosulfate, adrenalin, benadryl and others must be given; in spite of all precautions edema of the glottis may supervene, necessitating emergency tracheotomy.

Among the late reactions the pyrogenic ones are less frequent and less intense than in adults. Osteomyelitis is a rare complication of intramedullary transfusions if asepsis is strictly adhered to during the transfusion.

Symposium Section

Veratrum Viride in Hypertension

With the possible exception of ergot there probably was no more important drug in the obstetric bag of earlier practitioners who delivered babies in the home, than the tincture of veratrum viride. It was relied on to control the convulsions of eclampsia and there are many of the older group living today who have every reason to believe it was a lifesaver. Like most of the drugs of the early days of this century, tincture of veratrum viride like tincture of digitalis and tincture of ergot was not properly standardized and the effects were variable. This depended on the strength or weakness of the different tinctures, so it was impossible to estimate effective doses or foresee what might occur. The object of giving veratrum viride when labor was accompanied by convulsions was to "soften the pulse," which was full and bounding. There was no doubt that it would, but to what extent there was no way of predicting. If the patient recovered, its use was fully vindicated but if death followed it was assumed to be due to the toxemias of pregnancy which initiated the convulsions in the first place. In any event, as the study of pharmacology progressed and satisfactory biologic criteria were established to assay drugs and determine their dosage and effects in advance, veratrum viride was discarded as being too dangerous for general use. Unlike the tincture of digitalis it was not standardized in measurable units, so little was heard of it by present generations until recently.

Those who have aroused interest in veratrum viride in essential hypertension by their reports of clinical study cite that as early as 1915 Collins[1] observed the results of a single dose of what was probably the old tincture in hypertensive patients. He concluded that definite and often striking reductions in blood pressure could occur with the use of subtoxic doses but he made no attempt to treat his patients over long periods of time. The hypotensive effects of the drug, present day writers found, were confirmed by Wedd[2] and by Hewlett[3] but apparently Hite[4] is the first to report the treatment of hypertensive patients continuously for eight months and reach the conclusion that veratrum viride is a valuable therapeutic agent in this disease. Later Freis and associates[5] continued with another clinical study and their investigations of the hemodynamic effects of hypotensive drugs, which included veratrum viride,[6] clarified many of the physiologic effects of the drug and the factors which modify or change its action.

Renewed interest in veratrum viride, however, really began with the investigations of Craig and Jacobs[7] who isolated the veratrum alkaloids and found them to be sterol compounds related chemically to the digitalis glycosides, the steroid hormones and vitamin D. Then using the pure alkaloids, Krayer and his co-workers[8] demonstrated that subtoxic doses in experimental animals produced a vasodepressor response of a reflex nature. Following this experimental work came the study of Freis and associates[6] to determine the hemodynamic or other pharmacologic effects in human beings. Other contributions

1. Collins, R. J.: The Clinical Actions of Veratrum, *Arch. Int. Med.*, **16**:54, 1915. Cited by several of the recent writers.
2. Wedd, A. M.: Veratrum Viride in Auricular Fibrillation, *Heart*, **12**:307 (March) 1926.
3. Hewlett, A. W.: The Pulse Flow in the Brachial Artery. V. The Influence of Certain Drugs, *Arch. Int. Med.*, **20**:1 (July) 1917.
4. Hite, W. K.: Hypertension and Veratrum Viride, *Illinois M. J.*, **90**:336 (December) 1946.
5. Freis, E. D. and Stanton, J. R.: A Clinical Evaluation of Veratrum Viride in the Treatment of Essential Hypertension, *Am. Heart J.*, **36**:723 (November) 1948.
6. Freis, E. D., Stanton, J. R., Culbertson, J. W., Litter, J., Halperin, M. H., Burnett, C. H. and Wilkins, R. W.: The Hemodynamic Effects of Hypotensive Drugs in Man. I. Veratrum Viride, *J. Clin. Investigation*, **28**:353 (March) 1949.
7. Craig, L. C. and Jacobs, W. A.: The Veratrine Alkaloids. XX. Further Correlations in the Veratrine Group. The Relationship Between the Veratrine Bases and Solanidine, *J. Biol. Chem.*, **149**:451, 1943.
8. Krayer, O. and Acheson, G. H.: The Pharmacology of the Veratrum Alkaloids, *Physiol. Rev.*, **26**:383 (July) 1946.

have been made by Wilkins[9] and by Meilman and Krayer.[10]

Among the currently available preparations of veratrum viride is a stabilized powder known as "Vertavis."* It is an extract of the alkaloids and is regarded by Freis, Wilkins and others as being a stabilized product of fairly uniform potency, biologically standardized so that each tablet contains 10 "Craw units." This preparation is put up in tablet form for oral administration. Another preparation for parenteral administration, known as "Veratrone"† has been used by Freis and others. This preparation is injected intramuscularly. Another preparation, Veriloid, has been described by Stutzman, Maison and Kusserow,[11] but Wilkins,[9] who cites their work, states that it is still in the status of an experiment and is not available commercially.

In addition to the isolation of veratrum alkaloids, their biologic standardization was quite necessary before they could be offered for general use. Different species of small animals, such as frogs, mice, rats, pigeons, guinea pigs and rabbits, were used but eventually a genus of fresh water crustaceans, *Daphnia magna*, a type of fresh water flea which has been used occasionally in biologic studies proved more satisfactory than any. A unit which is now generally known as the Craw unit,‡ after the worker who developed this method of assay at the laboratories of Irwin, Neisler and Company of Decatur, Illinois, was adopted. The dose of preparations which are available at the present time is measured in these units even though Maison and Stutzman are at present experimenting on larger animals.

9. Wilkins, R. W.: *Veratrum Viride* and Essential Hypertension, *New England J. Med.*, **242**:535 (April 6) 1950. See page 74.
10. Meilman, E. and Krayer, O.: Clinical Studies on Veratrum Alkaloids. I. The Action of Protoveratrine and Veratridine in Hypertension. *Circulation*, **1**:204 (February) 1950.
11. Stutzman, J. W., Maison, G. L. and Kusserow, G. W.: Veriloid, a New Hypotensive Extract of Veratrum Viride, *Proc. Soc. Exper. Biol. & Med.*, **71**:725 (August) 1949.

* Product of Irwin, Neisler & Company, Decatur, Illinois.

† Product of Parke, Davis & Company, Detroit, Michigan.

‡ A Craw unit is the amount of Vertavis necessary to produce systolic arrest of the daphnia heart.

Freis and his associates in their clinical studies have used a therapeutic dose of Vertavis, which is the preparation of veratrum viride they used, of 10 to 40 Craw units in those patients who responded to the drug. They found that on increasing the dosage beyond this point further reduction of blood pressure occurred, but it inevitably led to toxic reactions. The margin between the therapeutic and the toxic doses usually was no greater than 10 Craw units. For any given individual the effective dose could be determined only by trial with gradually increasing doses. The therapeutic dose bore no relation to the surface area of the patients or the severity and duration of the disease. If the effective dose was greater than 10 Craw units, ingestion of the total dose at one time frequently resulted in side reactions, particularly nausea and vomiting. However, by subdividing the total effective dose so that no more than 10 Craw units were administered at hourly intervals, these side reactions were reduced considerably. Although there was great individual variation in the size of the effective dose (considered by Freis and Stanton to be a dose which resulted in a reduction of 20 mm. in systolic and 15 mm. in diastolic pressure), the onset and duration of the hypotensive response were quite uniform in different patients. Quite consistently, after the oral administration of veratrum viride, the hypotensive effect began to appear at the end of 1 or 2 hours, reached a maximum in 4 to 6 hours, and disappeared by the end of 14 hours.

Further to summarize the clinical observations of veratrum viride in the alleviation of essential hypertension, it may be said that it has proved useful in the treatment of patients with hypertensive crisis; severe, long-standing hypertensive disease which proved resistant to other forms of treatment and in hypertension complicated by cardiac failure. Prolonged therapy in some cases has resulted in a diminution in cardiac size and reversal of electrocardiographic changes toward normal. There have been no deaths and no toxic reactions resulting in more than transient disability attributable to the drug in the several series consulted for this brief review. All of these series were conducted under the careful supervision of staffs in medical centers,

who suggest that the development of side effects and changing of sensitivity to a given dose were sufficiently frequent to limit its usefulness in the treatment of patients with mild or moderate degrees of hypertension.

General impressions, which are gained from the carefully controlled clinical studies so far reported, are that the present standardized preparations of veratrum viride alkaloids available are at about the stage through which digitalis passed when it was undergoing the transition from the old tincture of digitalis to the many preparations which are now available but which still require discrimination in their use. In no article have we seen the present status of the drug expressed better than in a very recent one by Dr. Wilkins from the Evans Memorial, Massachusetts Memorial Hospitals and the Department of Medicine, Boston University School of Medicine. Dr. Wilkins is physician-in-chief of the Hypertension Clinic of these hospitals from which the studies of Freis and associates also came. Dr. Wilkins concludes that "*Veratrum viride* is effective in moderating the arterial pressure in essential hypertension. The oral preparations presently available may produce nausea, vomiting and even collapse unless extreme care is taken with the dosage, and occasionally may do so in spite of such care. Purified extracts and pure alkaloids have been produced for experimental trial, and may eliminate some of these objectionable side reactions. However, in any of its present available forms, *V. viride* is far from an ideal or a curative medicinal agent in essential hypertension. Nevertheless, it seems worthy of further investigation."

Aureomycin in Tick Typhus

The results of a clinical trial of the use of aureomycin in tick typhus are recorded by R. R. Henderson, R. K. A. van Someren, and K. E. R. Robertson (*East African Medical Journal,* April 1950, 27, 149). The report concerns 4 cases, including 1 child aged 8 years. The total dosage of aureomycin varied from 4 to 15 g., the drug being administered in 3 cases orally, and in 1 by intramuscular injection; in this last case a total dose of only 4 g. was used, with satisfactory results. Fever subsided within 72 hours, average, and the rash and headaches diminished with the fall in temperature. Side effects of the drug when taken by mouth were nausea and vomiting; but when given intramuscularly great pain followed the injection and spread to the rest of the limb. It is stated that "Aureomycin is an effective agent in the treatment of tick typhus . . . the rapid control of the infection appears to eliminate the risk of persisting tachycardia. . . No ill effects of the drug were noted up to 6 months after treatment."—*The Practitioner,* 165: 97 (July) 1950.

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Bornholm Disease and Coxsackie Virus

So far as we can see the only excuse for using the above title is to "hit the reader in the eye." It is reasonable to assume that not many know this old disease by this name, so it serves no useful purpose other than to inveigle the reader to read on. It has long been known to advertising and other kinds of writers that if they start with a vague slogan or an unusual sentence the attention of a browser may be ensnared. For example, there is the old bromide about Richard Harding Davis' advice to young writers. Davis it should be recalled was a popular writer of what more recently became known as the best-sellers. He reached the zenith of his popularity at about the turn of the century and was a source of inspiration to younger literary aspirants of the time. It is said that he would always emphasize the importance of gaining the attention of a reader in the first sentence. On one occasion a young admirer submitted: "Nuts, said the Queen, who hitherto had not taken part in the conversation," in response to Mr. Davis' request for curiosity-arousing first sentences. The youngster was doubtless inspired by unexpurgated editions of Canterbury Tales in which Chaucer vied with Queen Elizabeth and Sir Walter Raleigh in their allegedly foul fireside conversations. Those who have been fascinated by these early English risqué contributions could rewrite that sentence in many ways. We know we could but this has to go through the mails. Anyway that is why we used Bornholm Disease as a title.

We have always been opposed to calling a disease after an individual who first described it or after a geographic location where it first appeared. Such names never convey any information of the nature of a disease. Moreover, we have known men whose names have been associated with diseases who repeatedly asked that more descriptive names be adopted. One of these was Tom Cooley who never favored the term "Cooley's anemia." Then it became Mediterranean anemia because it was believed to be confined to Greeks and Italians on the north shore of this sea. But when proved cases were reported in a Chinese child, an East Indian and other nationalities far removed from the Riviera, many believed that erythroblastic anemia was more descriptive.

It seems curious that several British authors should have picked the term Bornholm Disease to discuss what most prefer to refer to as Epidemic Diaphragmatic Pleurodynia, in two[1, 2] articles which have appeared recently. This is probably due to the fact that they did not trace this disease back any further than 20 years ago when the Danish physician Ejnar Sylvest described an epidemic of myalgia among the inhabitants of some fishing villages on the island of Bornholm.

In order to keep the record of the curious outbreaks of this disease straight, it may be well to reveal that it has been occurring at irregular intervals in widely separated parts of the world ever since Prof. W. C. Dabney[3] first reported and clearly identified it at the University of Virginia and in Charlottesville in 1888. Ever since then the clinical pattern of the disease has followed a strikingly consistent sequence. It has appeared most often in epidemics and has been characterized chiefly by severe and sometimes agonizing pain around the midriff which is difficult to classify as diaphragmatic or pleuritic.*

1. Hopkins, J. H. S.: Bornholm Disease, *Brit. M. J.*, **1**: 1230 (May 27) 1950.
2. Findlay, G. M. and Howard, E. M.: Coxsackie Viruses and Bornholm Disease, *Brit. M. J.*, **1**: 1233 (May 27) 1950.
3. Dabney, W. C.: Account of an Epidemic Resembling Dengue Which Occurred in and Around Charlottesville and the University of Virginia in June, 1888, *Am. J. M. Sc.*, **96**: 488 (November) 1888.

* For clinical description see Editorial: Epidemic Pleurodynia, *Internat. M. Digest*, **50**: 119 (February) 1947.

So what better name could be selected than epidemic diaphragmatic pleurodynia. In any event many names were used before the Danish outbreak on Bornholm Island.

Interesting among these was one suggested by one of Dabney's patients. He likened the severe pain which occurred with each deep inspiration as "the devil's grip." So it was commonly called Devil's Grip for several years in Rappahannock County, Virginia. Most of our knowledge of the typical clinical course of the disease which resulted in the present day descriptive term dates from Dabney's report. But on previous occasions we[4] were able to go back much further, and strange enough we found that it was described by Scandinavians in the middle of the last century.

In 1856 and again in 1863, Finsen of Copenhagen, the father of heliotherapy, observed outbreaks of an epidemic disease in Iceland which he reported in 1874 as muscular rheumatism of the chest. About the same time a similar disease was described in Norway by Daae as an epidemic of acute muscular rheumatism spread by contagion. Then Homann described a similar outbreak in Norway which he called "Bamle disease" after the place where the first case occurred. Next the disease or a reasonable facsimile of it occurred in England, Finland, Sweden and Germany at irregular intervals.

Then about 25 years ago more reports came from this country on Cape Cod, in Philadelphia, New York, Cincinnati and southwestern Ohio and more recently in Brooklyn. For the most part, these and all previous articles have discussed the clinical course of the disease and its epidemiology and with few exceptions no idea of what caused the disease was advanced. These exceptions were vague references to the possibility of it being virus borne but no identifiable organism which could be associated with the disease has been discovered. Recently, however, in one of two papers by British authors under the title of Bornholm Disease, Findlay and Howard[2] have suggested that the "Coxsackie Virus" may prove to be the cause. The other paper by Hopkins reviews the clinical course of what he likewise calls Bornholm disease and reaches the conclusion that "since becoming familiar with the syndrome I have looked back over the last two years, and, from memory and notes, now realize that I have seen, but missed, many cases of Bornholm disease." This seems extraordinary but no more so than earlier statements in his opening paragraphs to the effect that "Bornholm disease, 'epidemic myalgia,' or 'epidemic pleurodynia,' has been recognized as a commonly occurring disease in the Scandinavian countries for about the last 20 years," and "the lack of familiarity with the disease is such that, as Hamburger and McNeil (1947) have suggested, it was still possible in 1944 for an epidemic to be reported as a 'new syndrome.' "

In any event, Findlay and Howard report the isolation of a virus closely resembling what has provisionally been called the Coxsackie virus from the blood, stools and nasal washings of a patient who developed typical symptoms of Bornholm disease. Thereupon they obtained serums from 20 patients who recently had been infected in small epidemics of the disease. In all cases the serums fixed complement in the presence of antigen made from one of the Coxsackie virus strains. Then serums from 14 out of 16 patients responded similarly with the same strains although their recent illnesses could not be fully established as having been the same disease. Again the use of a geographic name makes it necessary to explain that the Coxsackie strain is named after a small village 20 miles south of Albany, New York, but on the west bank of the Hudson River. It was isolated by Dalldorf and Sickles[5] of the New York State Health Department during the study of several small epidemics of poliomyelitis in upstate New York in the summer of 1947. It was described as an unidentified, filtrable agent isolated from the feces of children with paralysis during acute stages. Later Curnen, Shaw and Melnick[6] of Yale University Medical

4. Editorial: Epidemic Diaphragmatic Pleurodynia, *Internat. M. Digest*, **6**:60 (January) 1925; *ibid.*, **29**:56 (July) 1936; *ibid.*, **50**:119 (February) 1947; *ibid.*, **51**:247 (October) 1947 and *ibid.*, **52**:120 (February) 1948. Extensive bibliographies, which include references not listed here, are appended.

5. Dalldorf, G. and Sickles, G. M.: An Unidentified, Filtrable Agent Isolated from Feces of Children with Paralysis, *Science*, **108**:61 (July 16) 1948.

6. Curnen, E. C., Shaw, E. W. and Melnick, J. L.: Disease Resembling Nonparalytic Poliomyelitis Associated with a Virus Pathogenic for Infant Mice, *J. A. M. A.*, **141**:894 (November 26) 1949. Extensive bibliography appended.

School studied strains of a filtrable virus in New England obtained in the same way from nonparalytic patients. Several similar viruses have been studied including one by Sabin and Steigman[7] during an epidemic of "summer grippe."

However, the accelerated interest in viruses in general, since we have the means of growing and seeing them, forecasts a more hopeful outlook for a solution of the etiology of many diseases suspected of being virus borne. Poliomyelitis is definitely the most important and the more investigators study viruses the less elusive they will become. Howard and his associates[8] studied epidemic diaphragmatic pleurodynia in Brooklyn in 1942, conducted similar but more complete experiments than the British and certainly strengthened the suspicion that a virus or viruses may some day be established as the etiologic factor. Findlay and Howard[2] may have contributed further.

Meanwhile, it would help future investigators to locate the work of those who "blazed the trail" if it were indexed under more descriptive terms than the names of men or geographic locations.

7. Sabin, A. B. and Steigman, A. J.: Poliomyelitis Virus of Low Virulence in Patients with Epidemic "Summer Grippe or Sore Throat," *Am. J. Hyg.*, **49**:176 (March) 1949. Also see Editorial, Epidemic "Summer Grippe" and Poliomyelitis, *Internat. M. Digest*, **55**:122 (August) 1949.

8. Howard, T., Weymuller, C. A., Edson, J., Ittner, E., Watson, J. and Cassidy, M. L.: Epidemic Pleurodynia in Brooklyn in the Summer of 1942, *J. A. M. A.*, **121**:925 (March 20) 1943.

Asparagus and Its Characteristics

In *Bruxelles-Médical,* May 28, 1950, 30, 1190, there is an amusing note on an unusual topic entitled "L'Asperge." It is interesting to note that Suetonius, Martial, Galen and Dioscorides were familiar with the medicinal properties of asparagus, and that the roots and stems of this vegetable are used in pharmacy. The characteristic odour in the urine of those who have partaken of asparagus seems to have impressed Avicenna. "This disagreeable odour can be changed into a violet perfume by the simple addition of several drops of turpentine to the receiver which contains the urine." The physicians of the 18th century attributed its therapeutic virtues to the presence in its stems of much "ammoniacal and nitrous salt." Asparagus, however, does not suit everybody: this fact has been appreciated for a long time, and Boerhaave warned that it might promote an attack of gout, of haemoptysis, or haematuria. Nevertheless, according to Broussais, asparagus is a valuable cardiac sedative on account of its diuretic action.—*The Practitioner,* 165: 97 (July) 1950.